UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

PFIZER INC, ROBERT JARVIK, M.D., JARVIK HEART, INC., Plaintiffs, v. MATHEW I. GELFAND, M.D., Defendant.	x : : : : : : : : : : x	Civil Action No. 08 Civ. 2018 (LAK) (JCF) ECF case **AFFIDAVIT OF DAVID G. EBERT IN SUPPORT OF PLAINTIFFS' MOTION TO DISMISS DEFENDANT'S COUNTERCLAIMS**

STATE OF NEW YORK)
: ss.:
COUNTY OF NEW YORK)

DAVID G. EBERT, being duly sworn, deposes and says:

1. I am a member of Ingram Yuzek Gainen Carroll & Bertolotti, LLP, counsel for Pfizer Inc., Robert Jarvik, M.D., and Jarvik Heart, Inc ("Plaintiffs"). I have personal knowledge of the facts to which I attest and submit this affidavit in support of Plaintiffs' motion to dismiss defendant Mathew I. Gelfand, M.D.'s Counterclaims.

2. Copies of the following documents, to which Plaintiffs refer in the accompanying memorandum of law, are annexed:

Exhibit A	Complaint for Declaratory Judgment, dated February 28, 2008
Exhibit B	Defendant's Answer to Plaintiffs' Complaint for Declaratory Judgment and Defendant's Counterclaims against Plaintiffs for Patent Infringement, dated April 23, 2008
Exhibit C	Pfizer Inc. press release, "Pfizer Voluntarily Withdraws Lipitor Advertising Featuring Dr. Robert Jarvik," dated February 25, 2008
Exhibit D	FDA approval of supplemental New Drug Application for Lipitor®, dated September 30, 2003

Exhibit E	Lipitor® Label
Exhibit F	FDA approval of Pfizer Inc.'s New Drug Application for Caduet®, dated January 30, 2004
Exhibit G	Caduet® Label
Exhibit H	Contract between Pfizer Inc. and Robert Jarvik, M.D., dated April 13, 2006 (redacted)
Exhibit I	News Release, Committee on Energy and Commerce, "Committee Opens Investigation into Celebrity Drug Endorsements," dated January 7, 2008
Exhibit J	Letter from Rep. John D. Dingell and Rep. Bart Stupak to Pfizer Inc., dated January 7, 2008
Exhibit K	New York Times article, "Pfizer to End Lipitor Campaign by Jarvik," dated February 25, 2008
Exhibit L	News Release, Committee on Energy and Commerce, "Dingell, Stupak Comment on Pfizer Decision to Pull Lipitor Ads Featuring Dr. Jarvik," dated February 25, 2008

4. For the reasons stated in the accompanying memorandum of law, I respectfully urge the Court to grant Plaintiffs' motion in all respects.

DAVID G. EBERT

Sworn to before me this
16th day of May 2008

Notary Public

JOSEPHINE CABAN-ODIOT
Notary Public, State of New York
No. 01CA4705166
Qualified in Westchester County
Commission Expires Dec. 31, 2009

EXHIBIT A

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

PFIZER INC,
ROBERT JARVIK, M.D.,
JARVIK HEART, INC.,

Plaintiffs,

v.

MATHEW I. GELFAND, M.D.,

Defendant.

Civil Action No. 08-

COMPLAINT FOR DECLARATORY JUDGMENT

Pfizer Inc ("Pfizer"), Robert Jarvik, M.D. ("Dr. Jarvik") and Jarvik Heart, Inc., ("JHI") (collectively referred to as "Plaintiffs"), by their attorneys, for their complaint against Mathew I. Gelfand, M.D., ("Gelfand") allege as follows:

1. This is an action by Plaintiffs against Gelfand for a declaratory judgment of non-infringement, invalidity and unenforceability of United States Patent No. 5,837,688 ("the '688 patent"). A copy of the '688 patent is attached hereto as Exhibit A.

2. On November 17, 1998, the United States Patent and Trademark Office issued the '688 patent, entitled "Use of Thrombolytic Reagents for Prevention of Vascular Disease", on an application, Serial Number 758,615, filed by Gelfand on November 27, 1996.

PARTIES AND JURISDICTION

3. Pfizer Inc is a corporation organized and existing under the laws of the State of Delaware and has a place of business at 235 East 42nd Street, New York, New York 10017.

4. Dr. Jarvik is an individual residing in New York, New York and serves as President and Chief Executive Officer of JHI.

5. JHI is a New York Corporation, with offices located at 333 West 52nd Street, New York, New York 10019.

6. Upon information and belief, Gelfand is a resident of the State of New York, with an address of 245 Fairway Road, Lido Beach, New York 11561.

7. This is an action for a declaratory judgment of non-infringement, invalidity and unenforceability of the '688 patent and arises under the Patent Laws of the United States, Title 35, United States Code. This Court has subject matter jurisdiction over this action pursuant to the provisions of Title 28, United States Code §§ 1331, 1338, 2201 and 2202. An actual, substantial and continuing justiciable controversy exists between Plaintiffs and Gelfand regarding the alleged validity, enforceability and infringement of the '688 patent that requires a declaration of rights.

8. Gelfand is subject to personal jurisdiction in this District.

9. Gelfand has asserted to Plaintiffs in this District that he owns the '688 patent and that it claims a process by which a thrombolytic reagent with fibrinolytic activity is chronically administered to humans in low doses over long periods of time to treat vascular disease, including cardiovascular disease and cerebral vascular disease, *e.g.*, coronary heart disease, myocardial infarction or heart attack and stroke.

10. Gelfand has asserted in this District that Plaintiffs infringe the '688 patent by reason of their activities in manufacturing, promoting and selling two pharmaceutical products, Lipitor® and Caduet® and that he is entitled to an injunction and damages for such alleged infringement. Plaintiffs deny these allegations.

11. Pfizer, through Parke-Davis Pharmaceutical Research, a division of Warner-Lambert Company LLC, a wholly owned subsidiary of Pfizer, holds an approved New Drug Application from the FDA for an atorvastatin formulation which it sells and has been selling in the United States under the registered name Lipitor®.

12. Lipitor® was initially approved by the United States Food and Drug Administration ("FDA") for commercial marketing and sale on December 18, 1996.

13. Pfizer, through Parke-Davis Pharmaceutical Research, a division of Warner-Lambert Company LLC, a wholly owned subsidiary of Pfizer, holds an approved New Drug Application from the FDA for a combined atorvastatin and amlodipine formulation which it sells and has been selling in the United States under the registered name Caduet®.

14. Caduet® was initially approved by FDA for commercial marketing and sale on January 30, 2004.

CLAIM FOR RELIEF:
DECLARATORY JUDGMENT OF NON-INFRINGEMENT AND INVALIDITY OF THE '688 PATENT

15. Plaintiffs reallege paragraphs 1 through 14 above as if fully set forth herein.

16. This claim arises under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202, based upon an actual and substantial controversy between the parties.

17. Gelfand has asserted, and continues to assert, that Pfizer, Dr. Jarvik, and/or JHI have directly and indirectly infringed the '688 patent within the meaning of 35 U.S.C. § 271(a),

(b) and (e)(2)(A) by seeking FDA approval for and/or by making, offering for sale, selling, and inducing doctors and patients to use Lipitor® as a chronically administered thrombolytic reagent for the treatment or prevention of cardiovascular disease, including heart attack and stroke.

18. Gelfand has also asserted, and continues to assert, that Pfizer, Dr. Jarvik, and/or JHI have directly and indirectly infringed the '688 patent within the meaning of 35 U.S. C. § 271(a), (b) and (e)(2)(A) by seeking FDA approval for and/or by offering for sale, selling, and inducing doctors and patients to use Caduet® as a chronically administered thrombolytic reagent for the treatment or prevention of cardiovascular disease, including heart attack and stroke.

19. Gelfand has threatened to file suit in this District against Plaintiffs for alleged infringement of the '688 patent.

20. Plaintiffs deny each of Gelfand's allegations set forth in paragraphs 17-18 above and aver that they have the right to engage in making, offering for sale, selling, and promoting Lipitor® and Caduet® without license under the '688 patent.

21. On information and belief, the '688 patent is invalid for failure to comply with one or more conditions of patentability set forth in Part II of Title 35 of the United States Code, including but not limited to, 35 U.S.C.§§ 101, 102, 103 and/or 112.

22. The manufacture, sale, offer for sale, use, importation and promotion of Pfizer's Lipitor® has not and will not infringe, either literally or under the doctrine of equivalents, directly or indirectly, any valid, enforceable and unexpired claim of the '688 patent.

23. The manufacture, sale, offer for sale, use, importation and promotion of Pfizer's Caduet® has not and will not infringe, either literally or under the doctrine of equivalents, directly or indirectly, any valid, enforceable and unexpired claim of the '688 patent.

24. The '688 patent is unenforceable because it is being asserted by Gelfand and his attorneys against Plaintiffs without proper grounds or reasonable belief that any valid claim of the patent is or has been infringed, directly or indirectly, by the activities of Plaintiffs or any of them.

25. Gelfand and his attorneys know or should know that no valid claim of the '688 patent can be construed to cover any of Plaintiffs' activities, and the consequent misuse of the '688 patent renders it unenforceable against Plaintiffs and each of them.

26. Gelfand's undue delay in asserting his alleged patent rights bars any effort to enforce the '688 patent against Plaintiffs under the doctrines of laches and estoppel.

27. Plaintiffs are entitled to a declaration that the '688 patent is invalid.

28. Plaintiffs are entitled to a declaration that the manufacture, sale, offer for sale, use, importation and promotion of Pfizer's Lipitor® have not and will not infringe, either literally or under the doctrine of equivalents, directly or indirectly, any valid, enforceable and unexpired claim of the '688 patent.

29. Plaintiffs are entitled to a declaration that the manufacture, sale, offer for sale, use, importation and promotion of Pfizer's Caduet® have not and will not infringe, either literally or under the doctrine of equivalents, directly or indirectly, any valid, enforceable and unexpired claim of the '688 patent.

WHEREFORE, Plaintiffs request the following relief:

A. A declaratory judgment that the manufacture, sale, offer for sale, use, importation and promotion of Pfizer's Lipitor® have not and will not infringe, either literally or under the doctrine of equivalents, directly or indirectly, any valid, enforceable and unexpired claim of the '688 patent;

B. A declaratory judgment that the manufacture, sale, offer for sale, use, importation and promotion of Pfizer's Caduet® have not and will not infringe, either literally or under the doctrine of equivalents, directly or indirectly, any valid, enforceable and unexpired claim of the '688 patent;

C. A declaratory judgment that the '688 patent is invalid and unenforceable against Plaintiffs and each of them.

D. An award to Plaintiffs of their attorney fees, expenses and costs in defending against Gelfand's baseless allegations of infringement. Gelfand's assertions of infringement and its threats to seek damages and an injunction against Plaintiffs' future activities relating to Lipitor® and Caduet® were not designed or intended to protect or enforce any legitimate rights in the '688 patent but were undertaken for unrelated purposes and with knowledge that the '688 patent is invalid if construed to cover Plaintiffs' activities, thereby making this an "exceptional case" as defined in 35 U.S.C. § 285 entitling Plaintiffs to their reasonable attorney fees, expenses and costs. Moreover, Gelfand's counsel has, by making the threats against Plaintiffs, and will if continuing this case against Plaintiffs, engage in frivolous litigation, multiply the proceedings unreasonably and vexatiously, and thus will be personally liable for excess costs, expenses, and attorney fees incurred because of such conduct under 28 U.S.C. § 1927, and an award of those costs, expenses and attorney fees is requested; and;

E. Such further and other relief as this Court may deem just and proper.

Dated: February 28, 2008
New York, New York

INGRAM YUZEK GAINEN CARROLL & BERTOLOTTI, LLP

By: _____
David G. Ebert (DE 4078)
Attorneys for Plaintiffs Pfizer Inc., Robert Jarvik, M.D., and Jarvik Heart, Inc.
250 Park Avenue
New York, New York 10177
Telephone: (212) 907-9600
Facsimile: (212) 907-9681

OF COUNSEL:

Rudolf E. Hutz
Jeffrey B. Bove
Mary W. Bourke
William E. McShane
CONNOLLY BOVE LODGE & HUTZ LLP
1007 North Orange Street
Wilmington, DE 19899
Telephone: (302) 658-9141
Facsimile: (302) 658-5614

EXHIBIT A

US005837688A

United States Patent [19]

Gelfand

[11] Patent Number: 5,837,688

[45] Date of Patent: Nov. 17, 1998

[54] **USE OF THROMBOLYTIC REAGENTS FOR PREVENTION OF VASCULAR DISEASE**

[76] Inventor: Mathew I. Gelfand, 245 Fairway Rd., Lido Beach, N.Y. 11561

[21] Appl. No.: 756,615

[22] Filed: Nov. 27, 1996

[51] Int. Cl.[6] A61K 38/00

[52] U.S. Cl. 514/21; 514/2

[58] Field of Search 514/2, 21

[56] References Cited

U.S. PATENT DOCUMENTS

4,853,330	8/1989	Goeddel et al.	435/226
5,156,969	10/1992	Gill et al.	435/240.2
5,262,170	11/1993	Anderson et al.	424/94.64
5,288,503	2/1994	Wood et al.	424/497
5,385,732	1/1995	Anderson et al.	424/94.64
5,426,097	6/1995	Stern et al.	514/12

FOREIGN PATENT DOCUMENTS

297860 B1	4/1989	European Pat. Off. .
0 199 574	10/1991	European Pat. Off. .
0 297 860	9/1993	European Pat. Off. .

OTHER PUBLICATIONS

Bick et al., "Thrombolytic Therapy and Its Uses", Lab ,Med. 26:330–337, May 1995.

Shabahang et al., 1994, "The Clinical Impact of Risk Factor and Prophylaxis on Pulmonary Embolism", J. Vasc. Dis. 45:749–754.

Vipond et al., 1994, "Experimental Adhesion Prophylaxis with Recombinant Tissue Plasminogen Activator", Ann. R. Coll. Surg. Engl. 76:412–415.

Mohr et al., 1988, "Recent Advances in the Management of Venous Thromboembolism", Mayo Clin. Proc. 63:281–290.

Pannekoek et al., 1988, "Mutants of Human Tissue–Type Plasminogen Activator (t–PA): Structural Aspects and Functional Properties", Fibrinolysis 2:123–132.

Rose et al., 1986, "Plasminogen Activators", Ann. Rep. Med. Chem. 23:111–119.

Harris, 1987, "Second–Generation Plasminogen Activators", Prot. Eng. 1:449–458.

Fass and Toole, 1985, "Genetic Engineering and Coagulation Factors", Clin. Haem. 14:547–570.

Primary Examiner—Marianne M. Cintins
Assistant Examiner—Dwayne C. Jones
Attorney, Agent, or Firm—Pennie & Edmonds LLP

[57] **ABSTRACT**

The present invention relates to the administration of thrombolytic reagents such as tissue plasminogen activator (t-PA), streptokinase and/or urokinase, over prolonged periods of time for prevention of vascular disease such as cerebral vascular thrombosis, pulmonary embolism, deep venous thrombus, acute myocardial infarction and fresh or aged arterial thrombi. The invention relates generally to delivery systems that provide for sustained release of thrombolytic reagents such as tissue plasminogen activator (t-PA), streptokinase and/or urokinase, over prolonged periods of time. The thrombolytic reagents may be administered, for example, transdermally, topically, intranasally or orally.

17 Claims, No Drawings

USE OF THROMBOLYTIC REAGENTS FOR PREVENTION OF VASCULAR DISEASE

INTRODUCTION

The present invention relates to the administration of thrombolytic reagents such as tissue plasminogen activator (t-PA), streptokinase and/or urokinase, over prolonged periods of time for prevention of vascular disease such as cerebral vascular thrombosis, pulmonary embolism, deep venous thrombus, acute myocardial infarction and fresh or aged arterial thrombi. The invention relates generally to delivery systems that provide for sustained release of thrombolytic reagents such as tissue plasminogen activator (t-PA), streptokinase and/or urokinase, over prolonged periods of time. The thrombolytic reagents may be administered, for example, transdermally, topically, intranasally or orally.

BACKGROUND OF THE INVENTION

TISSUE PLASMINOGEN ACTIVATOR

Thrombolytic drugs act on the endogenous fibrinolytic system by converting plasminogen to the potent proteolytic enzyme plasmin. Plasmin in turn degrades fibrin clots and other plasma proteins. A number of thrombolytic drugs, including urokinase, streptokinase and t-PA, are currently used to treat acute vascular disease.

Tissue plasminogen activator (t-PA) activates plasminogen to generate the proteinase plasmin which plays an important role in the degradation of fibrin. t-PA has been a particularly important pharmaceutical agent for use in treatment of vascular diseases due to its ability to dissolve blood clots in vivo. t-PA was originally identified and purified from natural sources. Through the use of recombinant DNA techniques, DNA clones encoding the t-PA molecule have recently been identified and characterized leading to a determination of the DNA sequence and deduced amino acid sequence of t-PA (U.S. Pat. No. 4,853,330).

Several variants of t-PA have also been developed that address some of the disadvantages associated with the use of t-PA. These disadvantages include the short half life and fast clearance rate of t-PA. Such variants include those described in EPO Patent Publication No. 199,574, that have amino acid substitutions at the proteolytic cleavage sites at amino acid positions 275, 276 and 277. These forms are referred to as protease-resistant one-chain t-PA variants in that, unlike natural t-PA, they exist in either one chain or two chain form, are resistant to proteolytic cleavage and exist in one-chain form. Such variants are thought to be superior to natural t-PA for pharmaceutical uses in that they are more stable. In addition, a variety of glycosylation mutants exist at positions 117, 119, 184–186 and 448–450 which exhibit higher specific activity than natural t-PA.

A general review of plasminogen activators and derivatives thereof can be found in Harris (1987, Protein Engineering 1:449–458); Pannekoek et al. (1988, Fibrinolysis 2:123–132); and Ross et al. (1988, Annual Reports in Medicinal Chemistry, Vol. 23, Chapter 12), each of which is incorporated by reference herein.

VASCULAR DISEASE

Thrombosis and its complications are considered the most frequent causes of morbidity and death in the adult population. Pulmonary embolism is estimated to be the third most common cause of death in the United States (Mohr et al., 1988, Mayo Clin. Proc. 63:281–290). At present, anticoagulation is the basic approach to treatment of thromboembolic disorders (Bick, R. et al., 1995, Laboratory Medicine 26:330–337; Shabahang, M. et al., 1994, Angiology 45:749–754). Pharmaceutical preparations containing thrombolytic reagents such as t-PA, urokinase and streptokinase are currently used for treatment of acute vascular disease.

Short term administration of pharmaceutical preparations containing thrombolytic reagents, such as t-PA, urokinase or streptokinase, are currently used to treat patients suffering from cardiovascular diseases or conditions. For example, t-PA is parentally administered to patients as a means for treatment of deep vein thrombosis or peripheral vascular disease. t-PA is also used in connection with emergency medical care facilities for treatment of arterial embolisms which include pulmonary and extremity embolisms and infarction.

The deposition of fibrin in the peritoneal cavity may lead to fibrous adhesion formation which are the most common cause of small bowel obstruction in developed countries (Vipond et al., 1994, Ann. R. Coll. Surg. Engl. 76:412–415; EP 0297860 B1). t-PA has also been used successfully to prevent fibrin deposition or adhesion formation in the peritoneal cavity following surgery, infection, trauma or inflammation.

SUMMARY OF THE INVENTION

The present invention relates to methods for preventing vascular disease by the chronic administration of low doses of thrombolytic reagents such as tissue plasminogen activator (t-PA), streptokinase and/or urokinase, over prolonged periods of time. The present invention also relates to delivery systems that can be used in the methods of the invention. For example, systems that provide for sustained release of thrombolytic reagents, such as t-PA, over prolonged periods of time can be used. In general, the total daily dose range of t-PA should be sufficient to achieve serum concentrations of between about 1 and 50 mgs. For example, between about 1 and 50 mgs of a daily parenteral dose may be administered, most preferably a daily dose range should be between 10 and 30 mgs of t-PA. Therefore, an object of the invention is to provide dose-controlling applicators for thrombolytic compositions such as t-PA.

The present invention may be used therapeutically as a prophylactic means for inhibiting the development of vascular diseases such as pulmonary embolus, deep venous thrombus, acute myocardial infarction and fresh or aged arterial thrombi. The invention is of particular use for treatment of individuals at high risk for vascular disease, such as, diabetics, hypertensive or hypercholesterolemia patients, smokers or those individuals with a family history of vascular disease.

The present invention encompasses a number of preferred embodiments. In the first, the thrombolytic reagent is contained in a dermal patch which may be used to provide sustained release of tissue plasminogen activator into a patient's bloodstream over prolonged periods of time. In another embodiment of the invention the thrombolytic reagent may be combined with slow release gel formulations which may be applied topically to the patient. In yet another embodiment of the invention the thrombolytic reagent may be added to a biocompatible matrix material which may be implanted into the body of the patient for slow sustained release of the reagent. The thrombolytic reagent may also be administered orally or intranasally through the use of nasal sprays containing the reagent.

DETAILED DESCRIPTION OF THE INVENTION

Thrombosis and its complications are considered the most frequent causes of morbidity and death in the adult popu-

lation. The present invention involves a prophylactic method for inhibiting the development of vascular disease such as pulmonary embolus, deep venous thrombus and acute myocardial infarction and cerebral vascular thrombus. The invention relates to the chronic administration of low doses of thrombolytic reagents to prevent vascular disease. The thrombolytic reagents may be administered daily, weekly, monthly or yearly depending on the type of delivery system utilized. The desired goal of any such delivery systems is a constant long term delivery of thrombolytic reagents. Such thrombolytic reagents include, for example, t-PA, streptokinase and urokinase, etc.

The invention is of particular use for treatment of individuals at high risk for vascular disease, such as, diabetics, hypertensive or hyperlipidemia patients, smokers or those individuals with a family history of vascular disease. In such patients, the delivery of a continuous sustained release of thrombolytic reagents, such as t-PA, streptokinase or urokinase, may prevent the development of vascular disease.

Thus, the present invention relates to the chronic administration of low doses of thrombolytic reagents such as tissue plasminogen activator, streptokinase and/or urokinase over prolonged periods of time for prevention of vascular disease. The invention further relates to delivery systems that provide for long-term sustained release of thrombolytic reagents, such as t-PA, in the blood, which is effective as a means for preventing the development of vascular disease. The object of the invention is the prevention or dissolving of clots as they form in the vascular system of the treated patient. In accordance with the present invention, the object can be achieved through the use of t-PA preparations designed for sustained release of t-PA into the bloodstream of a patient over prolonged periods of time.

THROMBOLYTIC REAGENTS

The thrombolytic reagents to be used in the practice of the invention, herein defined as any reagents which have fibrinolytic activity, may be derived from a variety of different sources. For example, the t-PA may be produced in large quantities using recombinant DNA techniques well known to those skilled in the art such as those disclosed in U.S. Pat. No. 4,853,330 which is incorporated herein by reference. Alternatively, the t-PA may be obtained from a number of commercially available sources such as Activase© supplied by Genentech, Inc.

When using t-PA, it is within the scope of the invention that variants of naturally occurring t-PA may also be used in the practice of the invention. In preferred embodiments, such variants of t-PA may have an increased half life or a slower rate of clearance from the body. For example, variants having amino acid substitutions at the proteolytic cleavage sites at position 275, 276 and 277 which render t-PA preparations more stable may be used. Glycosylation mutants at amino acids 117–119, 184–186 and 448–45 exhibit a higher specific activity and such variant may also be used in the practice of the invention. t-PA can also be modified to delete amino acids 51–87 which results in a variant having a slower clearance from plasma. These variants represent only a subset of the known variants of t-PA which may be used in the presently claimed delivery systems.

It is also within the scope of the present invention that thrombolytic reagents other than t-PA may be used in the practice of the invention. Such agents include urokinase and streptokinase both of which may be obtained from commercial sources (Urokinase, Abbott Laboratories; Streptokinase, Pharmacia Adria).

METHOD OF PREVENTING VASCULAR DISEASE

The present invention relates to methods of preventing vascular disease by chronic administration of low doses of thrombolytic reagents. The present invention may be used as a prophylactic means for inhibiting the development of vascular diseases such as cerebral vascular thrombosis, pulmonary embolus, deep venus thrombus and acute myocardial infarction. The invention is of particular use for treatment of individuals at high risk for vascular diseases.

Pharmaceutical compositions suitable for use in the present invention include compositions wherein the thrombolytic ingredients are contained in an effective amount to achieve its intended purpose. More specifically, a therapeutically effective amount means an amount effective to prevent development of vascular disease in the subject being treated. A therapeutically effective dose refers to that amount of the compound that results in plasma levels of the thrombolytic reagent which are sufficient to maintain the beneficial modulating effects. Determination of the effective amounts is well within the capability of those skilled in the art.

The effective dose may be determined using a variety of different assays. For example, assays may be utilized to determine levels of fibrinogen or fibrin split products in the blood of treated patients. In such instances, the effective dose of the thrombolytic reagent is that amount required to sustain normal levels of fibrinogen or fibrin split products in the body of the patient. Such doses may be determined by measuring for levels of fibrinogen (assay for measuring levels of fibrinogen is available from M.L.A., Inc.) or fibrin split products (Thrombo-Wellco Test;MUREX, Inc.) in the blood of treated patients. A therapeutically effective dose refers to that amount of thrombolytic reagent sufficient to maintain normal circulating blood levels of about 2–4 mg/ml of fibrinogen, or, less than 10 mg/ml of fibrin split products.

The amount of composition administered will, of course, be dependent on the subject being treated, on the subject's weight, the severity of the affliction, the manner of administration and the judgment of the prescribing physician. It should be noted that the attending physician would know how to and when to terminate, interrupt or adjust therapy to lower dosage due to toxicity. Conversely, the attending physician would also know to adjust treatment to higher levels if the clinical response is not adequate (precluding toxicity).

In administering thrombolytic reagents to the patient, it is particularly important to monitor the patient for excessive bleeding or tendencies to bleed. A variety of different diagnostic tests, which are well known to those skilled in the art may be used to access the patients susceptibility to bleeding due to administration of the thrombolytic reagents. Such assays include a complete blood count (CBC), or a determination of prothrombin or partial prothrombin time.

The magnitude of a prophylactic dose of the t-PA in the management of vascular disease will vary with the patient to be treated and the route of administration. Again, it should be noted that the clinician or physician would know when to interrupt and/or adjust the treatment dose due to toxicity. The dose, and perhaps the dosage frequency, will also vary according to the age, body weight, and response of the individual patient.

In general, the total daily dose range of t-PA should be sufficient to achieve serum concentration levels ranging between 1 and 50 mgs. For example, between about 1 and 50 mgs of a daily parenteral dose may be administered, while most preferably a daily dose range should be between

about 10 and 30 mgs of a parenteral dose of t-PA. For smaller patients (less than 65 kg), a dose of 0.1–0.5 mg/kg may be administered daily. It is further recommended that infants, children, and patients over 65 years, and those with impaired renal, or hepatic function, initially receive low doses, and that they be titrated based on individual clinical response(s) and blood level(s). It may be necessary to use dosages outside these ranges in some cases as will be apparent to those of ordinary skill in the art.

THROMBOLYTIC DRUG DELIVERY SYSTEMS

A variety of drug delivery systems may be used to deliver the thrombolytic reagents, such as t-PA into the bloodstream of the patient. For example, the t-PA can be administered to a human patient in pharmaceutical compositions where it is mixed with suitable carriers or excipient(s) at doses therapeutically effective to prevent a variety of vascular disorders. Suitable routes of administration may, for example, include transdermal, topical, oral, intranasal and the like. Dosage forms include but are not limited to aerosol dispersions, creams, patches and the like.

For purposes of clarity, the following discussion describes delivery systems for t-PA. However, the delivery systems are not so limited. It is understood that the delivery systems described below may also be utilized for delivery of other thrombolytic reagents such as urokinase and streptokinase. Techniques for formulation and administration of the thrombolytic reagents of the instant application may be found in "Remington's Pharmaceutical Sciences," Mack Publishing Co., Easton, Pa., latest edition.

Pharmaceutical compositions for use in accordance with the present invention thus may be formulated in conventional manner using one or more physiologically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the t-PA into preparations which can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen. Suitable routes of administration may, for example, include transdermal, topical, oral, intranasal and the like. Dosage forms include but are not limited to aerosol dispersions, creams, patches and the like.

The formulations of the present invention normally will consist of t-PA with a carrier, or diluted by a carrier. Some examples of the diluents or carriers which may be employed in the pharmaceutical compositions of the present invention are lactose, dextrose, sucrose, sorbitol, mannitol, propylene glycol, liquid paraffin, white soft paraffin, kaolin, microcrystalline cellulose, calcium silicate, silica polyvinylpyrrolidone, cetostearyl alcohol, starch, gum acacia, calcium phosphate, cocoa butter, oil of theobroma, arachis oil, alginates, tragacanth, gelatin, syrup B.P., methyl cellulose, polyoxyethylene sorbitan monolaurate, ethyl lactate and propylhydroxybenzoate, sorbitan trioleate, sorbitan sesquioleate and oleyl alcohol.

Because of the short shelf life of t-PA in solution, formulations of t-PA in aqueous solutions, gels, etc. are stored under refrigeration to preserve the activity of the t-PA. Lyophilized preparations of t-PA may be stored at room temperature and protected from excessive exposure to light without loss of activity.

A variety of different drug delivery systems may be used to deliver t-PA into the bloodstream of the patient. In one particular embodiment of the invention a dermal patch may be used for sustained delivery of t-PA into the body. These membrane systems are designed to deliver controlled doses of drugs through the skin into the bloodstream.

TRANSDERMAL DELIVERY SYSTEM

Transdermal delivery of t-PA can be designed so that the rate of delivery of the t-PA closely follows the rate of clearance of the t-PA from the patient's body, thus keeping constant levels of the t-PA in the blood, thereby reducing t-PA waste and overdosing. The use of such a drug delivery system also provides a comfortable, convenient non-invasive method for unattended delivery of t-PA over a prolonged time period.

The transdermal patches to be used in the practice of the invention may be obtained from any of a variety of commercial sources. Most patches consists of a reservoir of drug material located behind a rate controlling membrane. The patch is impregnated with the t-PA and placed on the skin of the patient which allows the drug to penetrate readily into the body. In the practice of the invention the transdermal patch will be periodically replaced as the t-PA becomes depleted.

The transdermal patch is prepared to contain a solution of t-PA. The t-PA is dispersed in the solution, suspension or gel in a dissolved or undissolved state. The drug reservoir of the patch containing a solution, suspension or gel of t-PA also includes permeation enhancers which increase the skin penetration of the t-PA. Such permeation enhancers include those described in U.S. Pat. No. 4,573,966, which is incorporated by reference herein. Permeation enhancers may include plasticizer type enhancers such as lower alky and alkoxy esters of pharmaceutically acceptable fatty acids, fatty acid esters, fatty alcohols and similar hydrophobic compounds that are capable of increasing the permeability of drugs to the skin. In addition, solvent type enhancers may be used to increase the delivery of drugs through the skin. Such enhancers generally refer to relatively hydrophilic compounds having molecular weights of less than 200. More preferably, solvent type enhancers have a molecular weight of less than 150. They are also generally greater than 2 wt % soluble in water, and are preferably greater than 10 wt % soluble in water. Typically, solvent type enhancers include pharmaceutically acceptable lower alkyl alcohol, aryl alcohol, or polyol, for example, ethanol, propanol, butanol, benzyl alcohol, glycerin, or propylene glycol. as well as diluents, such as water or other additives. The solution of t-PA may be formulated to include vascular permeability factors (VPF's), as described in U.S. Pat. No. 5,503,843, which cause a rapid and reversible increase in blood vessel permeability. Such VPF may be added to the t-PA solution to facilitate the uptake of t-PA into the blood vessels of the skin. In addition, gelling agents may be added to increase the viscosity of the solution as is described in U.S. Pat. No. 5,503,843. The t-PA may also include diluents, stabilizers, biocides, antioxidants, anti-irritants and the like.

Because of the instability of t-PA in solution, it is desirable to design transdermal patches that can be stored at room temperature. Such a dermal patch may be designed, for example, with two compartments separated by a breakable barrier; one compartment contains lyophilized t-PA and the other compartment contains a solution or carrier, such as those described above, into which the t-PA is dissolved. Prior to the use of the patch, the barrier is broken, mixing the contents of both compartments thereby forming a drug reservoir containing a solution of t-PA. Alternatively, a transdermal patch may be designed with a single breakable compartment containing lyophilized t-PA, enclosed within the liquid carrier. Prior to use of the patch, the single compartment barrier is broken releasing the lyophilized t-PA into the carrier solution. The patch is then placed in contact with the skin in such a way that the drug reservoir containing the t-PA solution is in contact with the skin.

INTRANASAL DELIVERY SYSTEM

In yet another embodiment of the invention, the t-PA may be administered intranasally. The large blood supply carried in the capillaries of the nose allow drugs to enter the bloodstream quickly. For administration by inhalation, t-PA are conveniently delivered in the form of an aerosol spray

presentation from pressurized packs or a nebulizer, with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of e.g., gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

In addition, the inhalers may be formulated to include vascular permeability factors (VPFs) which cause an increase in blood vessel permeability thereby facilitating the uptake of t-PA into the blood vessels of the nose.

IMPLANTABLE DELIVERY SYSTEMS

In addition to the formulations described above, the t-PA may also be formulated as a slow release preparations that may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the t-PA may be formulated with suitable biocompatible matrix materials. The compounds may be delivered using a sustained-release system, such as slow release gel formations containing the t-PA. Various slow release gel formations have been established and are well known by those skilled in the art. Sustained-release capsules may, depending on their chemical nature, release the t-PA for prolonged periods of time.

ORAL FORMULATIONS

For oral administration, the compounds can be formulated readily by combining the active compounds with pharmaceutically acceptable carriers well known in the art. Such carriers enable the compounds of the invention to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a patient to be treated. Pharmaceutical preparations for oral use can be obtained solid excipient, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, and/or polyvinylpyrrolidone (PVP). If desired, disintegrating agents may be added, such as the cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures.

The t-PA is preferably formulated for oral administration with enteric coatings which protect the t-PA from enzymatic degradation in the stomach and promotes uptake by the intestinal tract. Such formulations are designed for slow release of t-PA through the intestinal wall and into the bloodstream of the patient. For example, the drug capsule containing t-PA may be coated with an enteric film which is sufficiently insoluble at a pH below 7 as to be capable of protecting the capsule and its contents from the digestive enzymes until the capsule reaches a region below the upper part of the intestine. Such film compositions include mixtures of anionic acrylic copolymers derived from at least on monomer selected from acrylic and methacrylic acids and methylacrylates. Such copolymers are commercially available under the trade name "Eudragit"(TM). Such enteric coatings are well known to those skilled in the art, and include those described in U.S. Pat. No. 4910021 and U.S. Pat. No. 5350741, each of which is incorporated by reference herein. Dyestuffs or pigments may also be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

Pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in a mixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added. All formulations for oral administration should be in dosages suitable for such administration.

For buccal administration, the compositions may take the form of tablets or lozenges formulated in a conventional manner.

PARENTERAL FORMULATIONS

The compounds may be formulated for parenteral administration by injection, e.g., by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, e.g., in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulator agents such as suspending, stabilizing and/or dispersing agents.

Pharmaceutical formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form. Additionally, suspensions of the active compounds may be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers or agents which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions.

Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use.

The compounds may also be formulated in rectal compositions such as suppositories or retention enemas, e.g., containing conventional suppository bases such as cocoa butter or other glycerides.

PACKAGING

The compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredient. The pack may for example comprise metal or plastic foil, such as a blister pack. The pack or dispenser device may be accompanied by instructions for administration. Compositions comprising a compound of the invention formulated in a compatible pharmaceutical carrier may also be prepared, placed in an appropriate container, and labelled for treatment of an indicated condition. Suitable conditions indicated on the label may include treatment of patients at risk for development of vascular diseases, or alternatively treatment of patients suffering from vascular diseases such as cerebral vascular

thrombosis, pulmonary embolism, deep venous thrombos, acute myocardial infarction and fresh or aged arterial thrombi.

EXAMPLE

TRANSDERMAL ADMINISTRATION OF THROMBOLYTIC REAGENTS

The following example describes the administration of the thrombolytic reagent t-PA utilizing a transdermal patch delivery system. The use of transdermal patches for the delivery of drugs through the skin is well known. Methods for the use of transdermal patches for delivery of drugs is described, for example, in the following United States patents, U.S Ser. Nos. 5,498,417, 5,503,844 and 5,503,843, each of which is incorporated by reference herein.

The following example illustrates the invention. It is not intended to limit the scope of the invention.

The t-PA (Activase, supplied by GENENTECH, Inc.) to be used in this example is supplied in 50 mg vials. The vials should be reconstituted in either sterile water or a pharmaceutical composition compatible with use in a transdermal patch.

The transdermal patch is prepared to contain a solution of t-PA. The t-PA is dispersed in the solution, suspension or gel in a dissolved or undissolved state. The drug reservoir of the patch containing a solution, suspension or gel of t-PA also includes permeation enhancers which increase the skin penetration of the t-PA. Such permeation enhancers include those described in U.S. Pat. No. 4,573,966, which is incorporated by reference herein. Permeation enhancers may include plasticizer type enhancers such as lower alky and alkoxy esters of pharmaceutically acceptable fatty acids, fatty acid esters, fatty alcohols and similar hydrophobic compounds that are capable of increasing the permeability of drugs to the skin. In addition, solvent type enhancers may be used to increase the delivery of drugs through the skin. Such enhancers generally refer to relatively hydrophilic compounds having molecular weights of less than 200. More preferably, solvent type enhancers have a molecular weight of less than 150. They are also generally greater than 2 wt % soluble in water, and are preferably greater than 10 wt % soluble in water. Typically, solvent type enhancers include pharmaceutically acceptable lower alkyl alcohol, aryl alcohol, or polyol, for example, ethanol, propanol, butanol, benzyl alcohol, glycerin, or propylene glycol as well as diluents, such as water or other additives. The solution of t-PA may be formulated to include vascular permeability factors (VPFs), as described in U.S. Pat. No. 5503843, which cause a rapid and reversible increase in blood vessel permeability. Such VPF may be added to the t-PA solution to facilitate the uptake of t-PA into the blood vessels of the skin.

The amount of t-PA contained in the patch is that amount necessary to deliver a daily dose of between 1–50 mg of t-PA. The treated patient's blood is monitored to determine the levels of circulating fibrinogen and/or fibrin split products. The amount of t-PA contained in the patch is adjusted so as to maintain blood levels of about 2–4 mg/ml of fibrinogen and 10 mg/ml of fibrin split products. In addition, the treated patient is monitored to prevent excessive bleeding which can result from treatment with thrombolytic reagents.

Once the transdermal patch has been prepared to contain an appropriate dose of t-PA, in a suitable solution, the patients skin is overlaid with the transdermal patch. The patch is placed in contact with the skin in such a way that the side of the patch containing the t-PA solution side is in contact with the patient's skin.

The present invention is not to be limited in scope by the specific embodiments described which are intended as single illustrations of individual aspects of the invention, and functionally equivalent methods and components are within the scope of the invention. Indeed, various modifications of the invention, in addition to those shown and described herein will become apparent to those skilled in the art from the foregoing description and accompanying drawings. Such modifications are intended to fall within the scope of the claims.

What is claimed:

1. A method for prevention of thrombotic vascular disease in a mammal, comprising the chronic administration to a patient in need thereof of an effective dose of a thrombolytic reagent to a mammal.

2. The method of claim 1 wherein the thrombolytic reagent is human tissue plasminogen activator.

3. The method of claim 1 wherein the thrombolytic reagent is streptokinase.

4. The method of claim 1 wherein the thrombolytic reagent is urokinase.

5. The method of claim 1 wherein the thrombolytic reagent is delivered in a transdermal patch.

6. The method of claim 5 wherein the thrombolytic reagent is selected from the group consisting of human tissue plasminogen activator, streptokinase and urokinase.

7. The method of claim 2 wherein the human tissue plasminogen activator is recombinant human tissue plasminogen activator.

8. The method of claim 1 wherein the thrombolytic reagent is delivered intranasally.

9. The method of claim 8 wherein the thrombolytic reagent is selected from the group consisting of human tissue plasminogen activator, streptokinase and urokinase.

10. The method of claim 1 wherein the thrombolytic reagent is delivered topically in a topical cream.

11. The method of claim 10 wherein the thrombolytic reagent is selected from the group consisting of human tissue plasminogen activator, streptokinase and urokinase.

12. The method of claim 1 wherein the thrombolytic reagent is delivered orally.

13. The method of claim 12 wherein the thrombolytic reagent is selected from the group consisting of human tissue plasminogen activator, streptokinase and urokinase.

14. The method of claim 1 wherein the dose of the thrombolytic reagent is that dose sufficient to maintain circulating blood levels of 2–4 mg/ml of fibrinogen or less than 10 mg/ml of fibrin split products.

15. The method of claim 1 wherein the dose of the thrombolytic reagent is that dose sufficient to maintain circulating blood levels of less than 10 mg/ml of fibrin split products.

16. The method of claim 2 wherein the daily dose of t-PA is between 1–50 mg.

17. The method of claim 2 wherein the daily dose of t-PA is between 10–30 mg.

* * * * *

EXHIBIT B

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

PFIZER INC, ROBERT JARVIK, M.D., JARVIK HEART, INC., Plaintiffs, v. MATHEW I. GELFAND, M.D., Defendant.	Civil Action No.: 08 CV 02018 **JURY TRIAL DEMANDED**

DEFENDANT'S ANSWER TO PLAINTIFFS' COMPLAINT FOR DECLARATORY JUDGMENT
AND
DEFENDANT'S COUNTERCLAIMS AGAINST PLAINTIFFS FOR PATENT INFRINGEMENT

Defendant Mathew I. Gelfand, M.D. ("Dr. Gelfand"), by and through his undersigned counsel, hereby respectfully files his Answer to Plaintiffs' Complaint for Declaratory Judgment ("Complaint") and his Counterclaims against Plaintiffs Pfizer, Inc. ("Pfizer"), Jarvik Heart, Inc. ("JHI"), and Robert Jarvik ("Jarvik") in this action, and states:

1. Paragraph 1 of the Complaint alleges one or more legal conclusions as to which no responsive pleading is required; to the extent that any facts are alleged therein, Dr. Gelfand denies them.

2. Admitted.

3. Admitted.

4. Admitted.

5. Admitted.

6. Admitted.

7. Paragraph 7 of the Complaint alleges one or more legal conclusions as to which no responsive pleading is required; to the extent that any facts are alleged therein, Dr. Gelfand denies them.

8. Admitted.

9. Admitted.

10. Admitted.

11. Dr. Gelfand admits that Pfizer holds a New Drug Application from FDA for an atorvastatin formulation which it sells and has been selling in the United States under the registered name Lipitor®, but lacks sufficient knowledge to form a belief about the truth of the balance of Paragraph 11.

12. Admitted.

13. Dr. Gelfand admits that Pfizer holds New Drug Application from FDA for an atorvastatin and amlodipine formulation which it sells and has been selling in the United States under the registered name Caduet®, but lacks sufficient knowledge to form a belief about the truth of the balance of Paragraph 13.

14. Admitted.

15. Dr. Gelfand's responses to paragraphs 1-14 of the Complaint are incorporated and referenced as though fully set forth herein.

16. Paragraph 16 of the Complaint alleges one or more legal conclusions as to which no responsive pleading is required; to the extent that any facts are alleged therein, Dr. Gelfand denies them.

17. Admitted.

18. Admitted.

19. Denied.

20. Paragraph 20 of the Complaint alleges one or more legal conclusions as to which no responsive pleading is required; to the extent that any facts are alleged therein, Dr. Gelfand denies them.

21. Paragraph 21 of the Complaint alleges one or more legal conclusions as to which no responsive pleading is required; to the extent that any facts are alleged therein, Dr. Gelfand denies them.

22. Paragraph 22 of the Complaint alleges one or more legal conclusions as to which no responsive pleading is required; to the extent that any facts are alleged therein, Dr. Gelfand denies them.

23. Paragraph 23 of the Complaint alleges one or more legal conclusions as to which no responsive pleading is required; to the extent that any facts are alleged therein, Dr. Gelfand denies them.

24. Paragraph 24 of the Complaint alleges one or more legal conclusions as to which no responsive pleading is required; to the extent that any facts are alleged therein, Dr. Gelfand denies them.

25. Paragraph 25 of the Complaint alleges one or more legal conclusions as to which no responsive pleading is required; to the extent that any facts are alleged therein, Dr. Gelfand denies them.

26. Paragraph 26 of the Complaint alleges one or more legal conclusions as to which no responsive pleading is required; to the extent that any facts are alleged therein, Dr. Gelfand denies them.

27. Paragraph 27 of the Complaint alleges one or more legal conclusions as to which no responsive pleading is required; to the extent that any facts are alleged therein, Dr. Gelfand denies them.

28. Paragraph 28 of the Complaint alleges one or more legal conclusions as to which no responsive pleading is required; to the extent that any facts are alleged therein, Dr. Gelfand denies them.

29. Paragraph 29 of the Complaint alleges one or more legal conclusions as to which no responsive pleading is required; to the extent that any facts are alleged therein, Dr. Gelfand denies them.

WHEREFORE, Defendant denies that he is liable to Plaintiffs, of any of them, for any ruling of law or thing of value whatsoever, and respectfully requests that Plaintiffs, and each of them, take nothing from Dr. Gelfand and that Plaintiffs, and each of them, be jointly and severally liable to Dr. Gelfand for a reasonable attorneys' fee and costs, including pursuant to 28 U.S.C. § 1927 and § 1928 and 35 U.S.C. § 285.

DR. GELFAND'S AFFIRMATIVE DEFENSES

1. The action brought by Plaintiffs against Dr. Gelfand is barred, in whole or in part, by the doctrine of estoppel.

2. The action brought by Plaintiffs against Dr. Gelfand is barred, in whole or in part, by the doctrine of fraud and/or misrepresentation.

3. The action brought by Plaintiffs against Dr. Gelfand is barred, in whole or in part, by the doctrine of unclean hands.

4. Dr. Gelfand incorporates by reference as affirmative defenses the allegations of his Counterclaims.

WHEREFORE, Dr. Gelfand respectfully requests that the judgment be entered in his favor against Plaintiffs and that Dr. Gelfand be awarded his attorney's fees and costs, including pursuant to 28 U.S.C. § 1927 and § 1928 and 35 U.S.C. § 285, together with such other or further relief, as this Court deems just and proper.

DEFENDANT DR. GELFAND'S COUNTERCLAIMS

Defendant Mathew I. Gelfand, M.D., ("Dr. Gelfand"), by and through his undersigned counsel, hereby files his counterclaims against Plaintiffs Pfizer Inc. ("Pfizer"), Robert Jarvik ("Jarvik"), and Jarvik Heart, Inc. ("JHI") (together, "Counter-Defendants"), and states as follows:

1. This is an action by Dr. Gelfand against Pfizer, Jarvik, and JHI for infringement of United States Patent No. 5,837,688 (hereinafter, the "'688 Patent").

PARTIES, VENUE, AND JURISDICTION

2. Dr. Gelfand is a practicing physician, licensed by the State of New York, with a specialty in internal medicine, hematology, and blood circulation. Dr. Gelfand is a citizen of New York, with an address at 245 Fairway Road, Lido Beach, New York, New York 11561.

3. Pfizer is a corporation organized and existing under the laws of the State of Delaware with a principal place of business at 235 East 42nd Street, New York, New York 10017.

4. Jarvik is world-renown medical engineer, is well-known among physicians who specialize in treating cardiovascular disease. Jarvik resides in New York, New York, and serves as President and Chief Executive Officer of JHI. Jarvik has never

been, and is not now, licensed to practice medicine in any state and he is not a cardiologist.

5. JHI is a New York corporation located at 333 West 52nd Street, New York, New York 10019, in business to promote treatment of cardiovascular disease, including coronary heart disease, in humans.

6. This action arises under the patent laws of the United States, Title 35, United States Code. This Court has subject matter jurisdiction over this action pursuant to 28 U.S.C. §§ 1331 and 1338(a).

7. Venue is proper in this District as to all Counter-Defendants pursuant to 28 U.S.C. § 1400(b) and, as to Counter-Defendants Pfizer and JHI, pursuant to 28 U.S.C. § 1391(b).

CONDITIONS PRECEDENT

8. Any and all conditions precedent for bringing or maintaining this cause of action have been satisfied by Dr. Gelfand, or are waived or excused by Counter-Defendants, and each of them.

FACTS

9. On application Serial Number 758,615, filed by Dr. Gelfand on November 27, 1996, the United States Patent and Trademark Office issued the '688 Patent, entitled "Use of Thrombolytic Reagent for Prevention of Vascular Disease," on November 17, 1998. A copy of the '688 Patent is attached hereto as Exhibit A and incorporated herein as if stated in full.

10. Pursuant to the '688 Patent, Dr. Gelfand owns and controls the right to preclude others, including Pfizer, Jarvik, and JHI, from practicing, from selling, and from

inducing the sale of a process by which a thrombolytic reagent with fibrinolytic activity is chronically administered to humans in low doses over long periods of time to treat vascular disease, including cardiovascular disease and cerebral vascular disease, *e.g.*, coronary heart disease, myocardial infarction or heart attack, and stroke.

11. The '688 Patent defines such thrombolytic reagents as drugs that reduce blood clots and, therefore, induce angiogenesis, *i.e.*, "drugs that act on the endogenous fibrinolytic system by converting plasminogen to the potent proteolytic enzyme plasmin. Plasmin in turn degrades fibrin clots and other plasma proteins."

12. The thrombolytic reagents that can be used in the practice of the '688 Patent includes "thrombolytic reagents such as tissue plasminogen activator" (t-PA) and, more broadly, all "delivery systems that provide for long-term sustained release of thrombolytic reagents, such as t-PA, in the blood, which is effective as a means for preventing the development of vascular disease."

13. As stated in the '688 Patent:

> The object of the invention is the prevention or dissolving of clots as they form in the vascular system of the treated patient. In accordance with the present invention, the object can be achieved through the use of t-PA preparations designed for sustained release of t-PA into the bloodstream of a patient over prolonged periods of time.

14. At the time that the '688 Patent became effective, it was generally accepted in the field of medicine: (a) that the human fibrinolytic system basically consists of a balance between clotting factors, such plasminogen activator inhibitor type 1 ("PAI-1"), and anti-clotting factors, such as t-PA; and (b) that an increase in t-PA activity in the blood and/or endothelial cells results in a decrease of PAI-1 activity therein as well.

15. On or about December 18, 1996, the United States Food and Drug Administration ("FDA") approved Pfizer's application for the sale of a statin product, the calcium salt of atorvastatin or "atorvastatin calcium," which compound Pfizer thereafter has sold and sells, and offered and offers for sale, in interstate commerce as Lipitor®. In 2002, FDA approved Pfizer to market doses of Lipitor® at doses as low as 10mg per day.

16. On September 30, 2003, Pfizer submitted to FDA a Supplemental New Drug Application ("SNDA") for Lipitor® "based on the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) lipid lowering arm results."

17. Dr. Gelfand first received the SNDA on January 25, 2008, after a three-year delay from FDA on his Freedom of Information Act request of September 26, 2005.

18. In its September 2003 SNDA for Lipitor®, Pfizer stated that the ASCOT lipid-lowering test results "support[] a new indication for the prevention of cardiovascular disease in patients without clinically evident coronary heart disease."

19. Pfizer further stated that the ASCOT lipid-lowering test results showed that Lipitor® at 10mg tablets conferred "additional protection" against coronary heart disease. Pfizer wrote to FDA:

> On September 2, 2002, the Data Safety Monitoring Board (DSMB) of ASCOT proposed to the Steering Committee that the double-blind lipid-lowering arm of ASCOT be terminated due to a highly significant reduction in the primary endpoint of coronary heart disease and a significant reduction in stroke incidence in those patients receiving Lipitor compared to a placebo. The magnitude of the benefit exceeded the predefined stopping rule for this part of the trial. The ASCOT Steering Committee accepted this recommendation on October 4, 2002 and a decision to close this section of the study was taken.

20. Since at least 2003, physicians treating patients for risks associated with cardiovascular and/or cerebral vascular disease, including coronary heart disease and

stroke, have known that blood clotting is the major risk factor for the occurrence of heart attack and stroke and that vascular angiogenesis is the major risk prevention factor for the occurrence of heart attack and stroke.

21. Since at least 2003, medical literature published in the United States has explored and extolled the benefits of statin compounds, including Lipitor®, for their benefit as a chronically administered or sustained-release thrombolytic and fibrinolytic reagent.

22. The thrombolytic and fibrinolytic properties of Lipitor® are the only medically reasonable explanation for the statements that Pfizer made to FDA in Pfizer's September 2003 SNDA to FDA about the effects of Lipitor® beyond cholesterol-lowering.

23. At some time after September 2003, Pfizer began a highly successful national marketing campaign for the sale of Lipitor® for its effect as a chronically administered or sustained-release thrombolytic and fibrinolytic reagent. In 2006 alone, Americans filled more than 79 million prescriptions for Lipitor®, accounting for roughly $14 billion in domestic sales of Lipitor®.

24. As early as September 2003, and as a material part of its national campaign to promote Lipitor®, Pfizer actively induced the infringement of the '688 Patent by inducing physicians in the United States to prescribe Lipitor®, and patients to use Lipitor®, for its effects beyond cholesterol-lowering, *i.e.*, as a chronically administered thrombolytic reagent in the treatment or prevention of cardiovascular disease, including heart attack and stroke.

25. In 2004, Pfizer obtained approval from FDA and began to manufacture, sell, and offer for sale a compound drug with trade name Caduet®, a drug that combines Pfizer's atorvastatin calcium (Lipitor®) with Pfizer's amlodipine product (Norvasc®) to treat cardiovascular disease.

26. In 2004, the American Journal of Hypertension ("AJH") reported:

> Data from the recent Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) support the view that statins protect hypertensive patients from end-organ damage, not only through cholesterol reduction but also through other pathways. These include a direct modulation of the endothelial function, as well as an interaction with the fibrinolytic activity. In this regard, evidence from in vitro studies indicate [*sic*] that statins positively affect the fibrinolytic system of cultured smooth muscle cells as well as endothelial cells.

(footnotes omitted). The AJH report is attached hereto as Exhibit B.

27. The AJH report concluded in material part:

(a) that "amlodipine monotherapy . . . significantly increased t-PA activity" in the human vascular system;

(b) that "atorvastatin monotherapy (ie, a significant decrease in PAI-1 activity and an increase in t-PA activity) confirm the findings of some in vitro and in vivo studies"; and

(c) that "the combination of amlodipine and atorvastatin improved the fibrinolytic balance more than the single monotherapy."

28. On August 5, 2005, Dr. Gelfand put Pfizer on notice that its manufacture, use, and sale of Lipitor® infringes on the '688 Patent. In his letter, Dr. Gelfand offered Pfizer the opportunity to license the '688 Patent.

29. On September 14, 2005, Pfizer responded to Dr. Gelfand's notice as follows:

> Lipitor has no indications that are dependent upon anti-thrombotic or fibrinolytic activity and there is no plan to pursue such an indication. The Pfizer team therefore concluded that [the '688 Patent] would have minimal value to Pfizer and there was no interest in further discussing this licensing opportunity.

The September 14, 2005, Letter from Ann C. Barry, Ph.D., Pfizer's Director of Licensing & Development, is attached hereto as Exhibit C ("Barry Letter"), and is incorporated herein as if stated in full.

30. Through the Barry Letter, Pfizer intentionally misrepresented its promotion of Lipitor®, its September 2003 SNDA to FDA for Lipitor®, and its plans for promoting Lipitor® and Caduet®.

31. Dr. Gelfand relied on Pfizer's misrepresentations to his detriment by not filing this suit prior to his receipt in January 2008 of Pfizer's September 2003 SNDA for Lipitor®. The SNDA reveals Pfizer's lie in the Barry Letter, Pfizer's bad faith towards Dr. Gelfand from as early September 2005 (if not before), and Plaintiffs/Counter-Defendants' willful infringement of the '688 Patent since September 2005.

32. On April 13, 2006, Jarvik entered into a two-year contract by which Jarvik is to receive $550,000 in the first year and $800,000 in the second year in return for his promotion of Lipitor®, including for its effects beyond cholesterol-lowering, *i.e.*, as a chronically administered thrombolytic reagent in the treatment or prevention of cardiovascular disease, including heart attack and stroke.

33. On information and belief, Jarvik has all or nearly all sums due under the initial two-year contract with Pfizer.

34. In his contract with Pfizer, Jarvik reserved control of his association with Pfizer's promotion of Lipitor®. Jarvik reserved "the right, in [his] discretion, to refuse

to have a statement attributed to [Jarvik] if [he] believes in good faith that such statement is untrue."

35. Jarvik has exercised that control. Jarvik and JHI have stated publicly:

> I have the training, experience, and medical knowledge to understand the conclusions of the extensive clinical trials that have been conducted to study the safety and effectiveness of Lipitor. Also, Pfizer submits advertising concepts in advance to the FDA for review and comment. The statements included in the ads fairly represent the scientific truth about Lipitor, which the public has a right to know, and which Pfizer is entitled to teach.
>
> I accepted the role of spokesman for Lipitor because I am dedicated to the battle against heart disease . . . . I believe the process of educating the public is beneficial to many patients and I am pleased to be part of an effort to reach them.
>
> I am not a celebrity. I am a medical scientist specializing in advanced technology to treat heart failure who understands that no one in his or her right mind would want an artificial heart if it could be avoided with preventive medicine.

36. For its part in its contract with Jarvik, Pfizer reserved the right to promote Lipitor® in ways that satisfies Jarvik: "In the event [Pfizer], in its sole discretion, requests approval from [Jarvik] with respect to any materials or any particular element, [Jarvik] shall provide comments, if any, in writing, within twenty-four (24) hours of [Jarvik's] receipt of such materials or element. In connection with the preceding sentence, [Jarvik] shall have the right to review all press releases prior to the general commercial distribution of such releases."

37. Pfizer prepared, and Jarvik approved, either tacitly or in writing, those advertisement that feature Jarvik's endorsement and promotion of Lipitor® for its effects beyond cholesterol-lowering, *i.e.*, as a chronically administered thrombolytic reagent in the treatment or prevention of cardiovascular disease, including heart attack and stroke.

38. The benefits that Jarvik has received by his promotion of Lipitor® for its effects beyond cholesterol-lowering *i.e.*, as a chronically administered thrombolytic reagent in the treatment or prevention of cardiovascular disease, including heart attack and stroke, include heightened medical, media, and financial attention for JHI.

39. Since not later than April 2006, Pfizer and/or Jarvik have, directly and indirectly, urged physicians and their patients at risk for heart attack and/or stroke to use Lipitor® for its effects beyond cholesterol-lowering, *i.e.*, as a chronically administered thrombolytic reagent in the treatment or prevention of cardiovascular disease, including heart attack and stroke. Such inducements include, without limitation:

(a) On October 15, 2006, Pfizer's President's J. Patrick Kelly was quoted in The New York Times: "By taking any dose of Lipitor, you will reduce the risk of a cardiovascular event faster and to a greater degree than you will with any other medicine."

(b) On September 7, 2006, the Boston Globe reported that Pfizer has sent thousands of sale representatives to convince physicians that Lipitor® is more effective in the prevention of heart disease than any other or generic statin.

(c) Beginning in 2006, Counter-Defendants began to run advertisement LP27879-I, and others like it, in major national newspapers. The newspaper advertisements features Jarvik, who extols Lipitor® for its effects beyond cholesterol-lowering, *i.e.*, as a chronically administered thrombolytic reagent in the treatment or prevention of cardiovascular disease, including heart attack and stroke.

(d) Beginning in 2006, Counter-Defendants began to run television and internet or web advertisements for Lipitor®. These advertisements feature Jarvik

extolling Lipitor® for its effects beyond cholesterol-lowering, *i.e.*, as a chronically administered thrombolytic reagent in the treatment or prevention of cardiovascular disease, including heart attack and stroke.

40. From time to time since September 2003, Pfizer has directly and indirectly infringed on the '688 Patent by offering for sale, selling, and inducing doctors and their patients to use Lipitor® and Caduet® as a chronically administered thrombolytic reagent for the prevention of vascular disease, including without limitation as a chronically administered reagent for reducing or otherwise affecting blood clotting or the fibrinolytic system in patients at risk for heart disease and/or stroke.

41. From time to time since April 13, 2006, Jarvik, for his own benefit and for the benefit of JHI, has directly and indirectly infringed on the '688 Patent by offering for sale, selling, and inducing doctors and their patients to use Lipitor® as a chronically administered thrombolytic reagent for the prevention of vascular disease, including without limitation as a chronically administered reagent for reducing or otherwise affecting blood clotting or the fibrinolytic system in patients at risk for heart disease and/or stroke.

42. From time to time since April 13, 2006, JHI has, through Jarvik, directly and indirectly infringed on the '688 Patent by offering for sale, selling, and inducing doctors and their patients to use Lipitor® as a chronically administered thrombolytic reagent for the prevention of vascular disease, including without limitation as a chronically administered reagent for reducing or otherwise affecting blood clotting or the fibrinolytic system in patients at risk for heart disease and/or stroke.

43. On February 25, 2008, Dr. Gelfand made an attempt to resolve this dispute with Counter-Defendants by sending a written request for a meeting to Jarvik and to Allen Waxman, the General Counsel of Pfizer.

44. In response to Dr. Gelfand's request for a meeting, Counter-Defendants filed a complaint for declaratory judgment that commenced this action.

FIRST CLAIM FOR RELIEF:
COUNTER-DEFENDANTS' INFRINGEMENT OF THE '688 PATENT
IN VIOLATION OF 35 U.S.C. 271(a)

45. Dr. Gelfand realleges paragraphs 1 through 44 above as if fully set forth herein.

46. The '688 Patent is valid and enforceable, and has been since at least 2003 and throughout the period from April 13, 2006, to date.

47. In violation of 35 U.S.C. §271(a), Counter-Defendants, and each of them, have infringed and violated the '688 Patent by selling and offering to sell Lipitor® within the United States -- without authority of Dr. Gelfand -- for Lipitor®'s effects beyond cholesterol-lowering, *i.e.*, as a chronically administered thrombolytic reagent in the treatment or prevention of cardiovascular disease, including heart attack and stroke.

48. In violation of 35 U.S.C. §271(a), Counter-Defendants, and each of them, have infringed and violated the '688 Patent by selling and offering to sell Caduet® within the United States -- without authority of Dr. Gelfand -- for Caduet®'s effects beyond cholesterol-lowering, *i.e.*, as a chronically administered thrombolytic reagent in the treatment or prevention of cardiovascular disease, including heart attack and stroke.

49. Pfizer infringed the '688 Patent in bad faith and willfully, including through Pfizer's misrepresentations in the Barry Letter of September 2003.

50. As a result of Counter-Defendants' infringement of the '688 Patent, Dr. Gelfand has suffered substantial damages within the meaning of 35 U.S.C. §284.

51. Dr. Gelfand will be irreparably harmed if Counter-Defendants are not enjoined from infringing the '688 Patent.

SECOND CLAIM FOR RELIEF:
COUNTER-DEFENDANTS' ACTIVE INDUCING INFRINGEMENT OF THE '688 PATENT
IN VIOLATION OF 35 U.S.C. 271(b)

52. Dr. Gelfand realleges paragraphs 1 through 44 above as if fully set forth herein.

53. The '688 Patent is valid and enforceable, and has been since at least 2003 and throughout the period April 13, 2006, to date.

54. In violation of 35 U.S.C. §271(b), Counter-Defendants, and each of them, have actively induced doctors to infringe the '688 Patent by inducing such doctors to use, prescribe, and otherwise require their patients to purchase Lipitor® within the United States -- without authority of Dr. Gelfand – to secure Lipitor®'s effects beyond cholesterol-lowering, *i.e.,* as a chronically administered thrombolytic reagent in the treatment or prevention of cardiovascular disease, including heart attack and stroke.

55. In violation of 35 U.S.C. §271(b), Counter-Defendants, and each of them, have actively induced doctors to infringe the '688 Patent by inducing such doctors to use, prescribe, and otherwise require their patients to purchase Caduet® within the United States -- without authority of Dr. Gelfand – to secure Caduet®'s effects beyond cholesterol-lowering, *i.e.,* as a chronically administered thrombolytic reagent in the treatment or prevention of cardiovascular disease, including heart attack and stroke.

56. Pfizer infringed the '688 Patent in bad faith and willfully, including through Pfizer's misrepresentations in the Barry Letter of September 2003.

57 As a result of Counter-Defendants' infringement of the '688 Patent, Dr. Gelfand has suffered substantial damages within the meaning of 35 U.S.C. §284.

58. Dr. Gelfand will be irreparably harmed if Counter-Defendants are not enjoined from infringing Dr. the '688 Patent.

THIRD CLAIM FOR RELIEF:
COUNTER-DEFENDANT PFIZER'S INFRINGEMENT OF THE '688 PATENT IN VIOLATION OF 35 U.S.C. 271(e)(2)(A)

59. Dr. Gelfand realleges paragraphs 1 through 44 above as if fully set forth herein.

60. The '688 Patent is valid and enforceable, and has been since at least 2003 and throughout the period April 13, 2006, to date.

61. Pfizer's SNDA of September 2003 sought authority from FDA to promote Lipitor® for its effects beyond cholesterol-lowering, *i.e.*, as a chronically administered thrombolytic reagent in the treatment or prevention of cardiovascular disease, including heart attack and stroke.

62. Pfizer's NDA of 2004 sought authority from FDA to promote Caduet® for its effects beyond cholesterol-lowering, *i.e.*, as a chronically administered thrombolytic reagent in the treatment or prevention of cardiovascular disease, including heart attack and stroke.

63. Pfizer's SNDA of September 2003 constitutes an "application . . . described by section 505(b)(2)" of the Federal Food, Drug, and Cosmetic Act "for a drug

claimed" in the '688 Patent or "the use of which is claimed" in the '688 Patent, all within the meaning of 35 U.S.C. §271(e)(2)(A).

64. Pfizer's NDA of 2004 constitutes an "application . . . described by section 505(b)(2)" of the Federal Food, Drug, and Cosmetic Act "for a drug claimed" in the '688 Patent or "the use of which is claimed" in the '688 Patent, all within the meaning of 35 U.S.C. §271(e)(2)(A).

65. In submitting its SNDA of September 2003 to FDA, Pfizer infringed the '688 Patent in violation of 35 U.S.C. §271(e)(2)(A).

66. In submitting its NDA of 2004 to FDA, Pfizer infringed the '688 Patent in violation of 35 U.S.C. §271(e)(2)(A).

67. Counter-Defendant Pfizer infringed the '688 Patent in bad faith and willfully, including through Pfizer's misrepresentations in the Barry Letter of September 2003.

68. As a result of Plaintiffs/Counter-Defendants' infringement of the '688 Patent, Dr. Gelfand has suffered substantial damages within the meaning of 35 U.S.C. §284.

69. Dr. Gelfand will be irreparably harmed if Plaintiffs/Counter-Defendants are not enjoined from infringing the '688 Patent.

FOURTH CLAIM FOR RELIEF:
COUNTER-DEFENDANT PFIZER'S INFRINGEMENT OF THE '688 PATENT IN VIOLATION OF 35 U.S.C. 271(a)

70. Dr. Gelfand realleges paragraphs 1 through 44 above as if fully set forth herein.

71. The '688 Patent is valid and enforceable, and has been since at least 2003 and throughout the period from April 13, 2006, to date.

72. In violation of 35 U.S.C. §271(a), Pfizer has infringed and violated the '688 Patent by making Lipitor® within the United States -- without authority of Dr. Gelfand -- for Lipitor®'s effects beyond cholesterol-lowering, *i.e.*, as a chronically administered thrombolytic reagent in the treatment or prevention of cardiovascular disease, including heart attack and stroke.

73. In violation of 35 U.S.C. §271(a), Pfizer has infringed and violated the '688 Patent by making Caduet® within the United States -- without authority of Dr. Gelfand -- for Caduet®'s effects beyond cholesterol-lowering, *i.e.*, as a chronically administered thrombolytic reagent in the treatment or prevention of cardiovascular disease, including heart attack and stroke.

74. Pfizer infringed the '688 in bad faith and willfully, including through Pfizer's misrepresentations in the Barry Letter of September 2003.

75. As a result of Pfizer's infringement of the '688, Dr. Gelfand has suffered substantial damages within the meaning of 35 U.S.C. §284.

76. Dr. Gelfand will be irreparably harmed if Pfizer is not enjoined from infringing the '688 Patent.

WHEREFORE, Dr. Gelfand requests the following relief from Counter-Defendants, and each of them, as follows:

A. a judgment of the Court for damages against Counter-Defendants, jointly and severally, adequate to compensate Dr. Gelfand for Counter-Defendants' infringement of the '688 Patent, but not less than one percent (1%) of the net sales of Lipitor® for each

year commencing April 13, 2006 through the expiration of the '688 Patent plus 30 months (to compensate for time lost to Dr. Gelfand by Pfizer's misrepresentations in the Barry Letter), all as allowed by 35 U.S.C. §284;

B. a judgment of the Court for damages against Counter-Defendants, jointly and severally, adequate to compensate Dr. Gelfand for Counter-Defendants' infringement of the '688 Patent, but not less than one percent (1%) of the net sales of Caduet® for each year commencing April 13, 2006 through the expiration of the '688 Patent plus 30 months (to compensate for time lost to Dr. Gelfand by Pfizer's misrepresentations in the Barry Letter), all as allowed by 35 U.S.C. §284;

C. an order of this Court preliminarily and then permanently enjoining Pfizer from making Lipitor® and/or Caduet® until the expiration of the '688 Patent plus 30 months (to compensate for time lost to Dr. Gelfand by Pfizer's misrepresentations in the Barry Letter), all as allowed by 35 U.S.C. §283;.

D. an order of this Court preliminarily and then permanently enjoining Counter-Defendants from selling, offering for sale, or inducing the use of Lipitor® and/or Caduet® until the expiration of the '688 Patent plus 30 months (to compensate for time lost to Dr. Gelfand by Pfizer's misrepresentations in the Barry Letter), all as allowed by 35 U.S.C. §283;.

E. Treble damages as allowed by 35 U.S.C. §284;

F. Attorneys' fees in this action pursuant to 35 U.S.C. § 285 and 28 U.S.C. § 1927 and § 1928;

G. Costs and expenses in this action; and

H. Such further and other relief as this Court may deem just and proper.

JURY TRIAL DEMAND

Dr. Gelfand hereby demands trial by jury as to all issues triable as of right by jury.

Dated: April 23, 2008
Bethesda, Maryland

Respectfully Submitted,

THE ROTBERT LAW GROUP, LLC

/s/ Mitchell J. Rotbert
Mitchell J. Rotbert
Bar No. MR-0484
7315 Wisconsin Avenue
Suite 1250 West
Bethesda, Maryland 20814
Phone: (240) 333-4517
Fax: (301) 251-4032
mrotbert@rotbertlaw.net

Attorney for Plaintiff
Mathew I. Gelfand, M.D.

CERTIFICATE OF SERVICE

I HEREBY CERTIFY that, on this 23rd day of April, 2008, I caused a copy of the foregoing to be delivered via ECF filing and by United States Mail, postage prepaid, to:

David G. Ebert
INGRAM YUZEK GAINEN CARROLL & BERTOLOTTI, LLP
250 Park Avenue
New York, New York 10177
Counsel for Plaintiffs

Rudolf E. Hutz
Jeffrey B. Bove
Mary W. Bourke
CONNOLLY BOVE LODGE & HUTZ LLP
1007 North Orange Street
Wilmington, DE 19899
Of Counsel for Plaintiffs

/s/ Mitchell J. Rotbert
Mitchell J. Rotbert

EXHIBIT A

US005837688A

United States Patent [19]

Gelfand

[11] Patent Number: 5,837,688

[45] Date of Patent: Nov. 17, 1998

[54] USE OF THROMBOLYTIC REAGENTS FOR PREVENTION OF VASCULAR DISEASE

[76] Inventor: Mathew I. Gelfand, 245 Fairway Rd., Lido Beach, N.Y. 11561

[21] Appl. No.: 758,615

[22] Filed: Nov. 27, 1996

[51] Int. Cl.[6] A61K 38/00

[52] U.S. Cl. 514/21; 514/2

[58] Field of Search 514/2, 21

[56] References Cited

U.S. PATENT DOCUMENTS

4,853,330	8/1989	Goeddel et al.	435/226
5,156,969	10/1992	Gill et al.	435/240.2
5,262,170	11/1993	Anderson et al.	424/94.64
5,288,503	2/1994	Wood et al.	424/497
5,385,732	1/1995	Anderson et al.	424/94.64
5,426,097	6/1995	Stern et al.	514/12

FOREIGN PATENT DOCUMENTS

297860 B1	4/1989	European Pat. Off. .
0 199 574	10/1991	European Pat. Off. .
0 297 860	9/1993	European Pat. Off. .

OTHER PUBLICATIONS

Bick et al., "Thrombolytic Therapy and Its Uses", Lab ,Med. 26:330–337, May 1995.

Shabahang et al., 1994, "The Clinical Impact of Risk Factor and Prophylaxis on Pulmonary Embolism", J. Vasc. Dis. 45:749–754.

Vipond et al., 1994, "Experimental Adhesion Prophylaxis with Recombinant Tissue Ploasminogen Activator", Ann. R. Coll. Surg. Engl. 76:412–415.

Mohr et al., 1988, "Recent Advances in the Management of Venous Thromboembolism", Mayo Clin. Proc. 63:281–290.

Pannekoek et al., 1988, "Mutants of Human Tissue–Type Plasminogen Activator (t–PA): Structural Aspects and Functional Properties", Fibrinolysis 2:123–132.

Rose et al., 1988, "Plasminogen Activators", Ann. Rep. Med. Chem. 23:111–119.

Harris, 1987, "Second–Generation Plasminogen Activators", Prot. Eng. 1:449–458.

Bass and Toole, 1985, "Genetic Engineering and Coagulation Factors", Clin. Haem. 14:547–570.

Primary Examiner—Marianne M. Cintins
Assistant Examiner—Dwayne C. Jones
Attorney, Agent, or Firm—Pennie & Edmonds LLP

[57] ABSTRACT

The present invention relates to the administration of thrombolytic reagents such as tissue plasminogen activator (t-PA), streptokinase and/or urokinase, over prolonged periods of time for prevention of vascular disease such as cerebral vascular thrombosis, pulmonary embolism, deep venous thrombus, acute myocardial infarction and fresh or aged arterial thrombi. The invention relates generally to delivery systems that provide for sustained release of thrombolytic reagents such as tissue plasminogen activator (t-PA), streptokinase and/or urokinase, over prolonged periods of time. The thrombolytic reagents may be administered, for example, transdermally, topically, intranasally or orally.

17 Claims, No Drawings

USE OF THROMBOLYTIC REAGENTS FOR PREVENTION OF VASCULAR DISEASE

INTRODUCTION

The present invention relates to the administration of thrombolytic reagents such as tissue plasminogen activator (t-PA), streptokinase and/or urokinase, over prolonged periods of time for prevention of vascular disease such as cerebral vascular thrombosis, pulmonary embolism, deep venous thrombus, acute myocardial infarction and fresh or aged arterial thrombi. The invention relates generally to delivery systems that provide for sustained release of thrombolytic reagents such as tissue plasminogen activator (t-PA), streptokinase and/or urokinase, over prolonged periods of time. The thrombolytic reagents may be administered, for example, transdermally, topically, intranasally or orally.

BACKGROUND OF THE INVENTION

TISSUE PLASMINOGEN ACTIVATOR

Thrombolytic drugs act on the endogenous fibrinolytic system by converting plasminogen to the potent proteolytic enzyme plasmin. Plasmin in turn degrades fibrin clots and other plasma proteins. A number of thrombolytic drugs, including urokinase, streptokinase and t-PA, are currently used to treat acute vascular disease.

Tissue plasminogen activator (t-PA) activates plasminogen to generate the proteinase plasmin which plays an important role in the degradation of fibrin. t-PA has been a particularly important pharmaceutical agent for use in treatment of vascular diseases due to its ability to dissolve blood clots in vivo. t-PA was originally identified and purified from natural sources. Through the use of recombinant DNA techniques, DNA clones encoding the t-PA molecule have recently been identified and characterized leading to a determination of the DNA sequence and deduced amino acid sequence of t-PA (U.S. Pat. No. 4,853,330).

Several variants of t-PA have also been developed that address some of the disadvantages associated with the use of t-PA. These disadvantages include the short half life and fast clearance rate of t-PA. Such variants include those described in EPO Patent Publication No. 199,574, that have amino acid substitutions at the proteolytic cleavage sites at amino acid positions 275, 276 and 277. These forms are referred to as protease-resistant one-chain t-PA variants in that, unlike natural t-PA, they exist in either one chain or two chain form, are resistant to proteolytic cleavage and exist in one-chain form. Such variants are thought to be superior to natural t-PA for pharmaceutical uses in that they are more stable. In addition, a variety of glycosylation mutants exist at positions 117, 119, 184–186 and 448–450 which exhibit higher specific activity than natural t-PA.

A general review of plasminogen activators and derivatives thereof can be found in Harris (1987, Protein Engineering 1:449–458); Pannekoek et al. (1988, Fibrinolysis 2:123–132); and Ross et al. (1988, Annual Reports in Medicinal Chemistry, Vol. 23, Chapter 12), each of which is incorporated by reference herein.

VASCULAR DISEASE

Thrombosis and its complications are considered the most frequent causes of morbidity and death in the adult population. Pulmonary embolism is estimated to be the third most common cause of death in the United States (Mohr et al., 1988, Mayo Clin. Proc. 63:281–290). At present, anticoagulation is the basic approach to treatment of thromboembolic disorders (Bick, R. et al., 1995, Laboratory Medicine

26:330–337; Shabahang, M. et al., 1994, Angiology 45:749–754). Pharmaceutical preparations containing thrombolytic reagents such as t-PA, urokinase and streptokinase are currently used for treatment of acute vascular disease.

Short term administration of pharmaceutical preparations containing thrombolytic reagents, such as t-PA, urokinase or streptokinase, are currently used to treat patients suffering from cardiovascular diseases or conditions. For example, t-PA is parentally administered to patients as a means for treatment of deep vein thrombosis or peripheral vascular disease. t-PA is also used in connection with emergency medical care facilities for treatment of arterial embolisms which include pulmonary and extremity embolisms and infarction.

The deposition of fibrin in the peritoneal cavity may lead to fibrous adhesion formation which are the most common cause of small bowel obstruction in developed countries (Vipond et al., 1994, Ann. R. Coll. Surg. Engl. 76:412–415; EP 0297860 B1). t-PA has also been used successfully to prevent fibrin deposition or adhesion formation in the peritoneal cavity following surgery, infection, trauma or inflammation.

SUMMARY OF THE INVENTION

The present invention relates to methods for preventing vascular disease by the chronic administration of low doses of thrombolytic reagents such as tissue plasminogen activator (t-PA), streptokinase and/or urokinase, over prolonged periods of time. The present invention also relates to delivery systems that can be used in the methods of the invention. For example, systems that provide for sustained release of thrombolytic reagents, such as t-PA, over prolonged periods of time can be used. In general, the total daily dose range of t-PA should be sufficient to achieve serum concentrations of between about 1 and 50 mgs. For example, between about 1 and 50 mgs of a daily parenteral dose may be administered, most preferably a daily dose range should be between 10 and 30 mgs of t-PA. Therefore, an object of the invention is to provide dose-controlling applicators for thrombolytic compositions such as t-PA.

The present invention may be used therapeutically as a prophylactic means for inhibiting the development of vascular diseases such as pulmonary embolus, deep venous thrombus, acute myocardial infarction and fresh or aged arterial thrombi. The invention is of particular use for treatment of individuals at high risk for vascular disease, such as, diabetics, hypertensive or hyperlipidemia patients, smokers or those individuals with a family history of vascular disease.

The present invention encompasses a number of preferred embodiments. In the first, the thrombolytic reagent is contained in a dermal patch which may be used to provide sustained release of tissue plasminogen activator into a patient's bloodstream over prolonged periods of time. In another embodiment of the invention the thrombolytic reagent may be combined with slow release gel formulations which may be applied topically to the patient. In yet another embodiment of the invention the thrombolytic reagent may be added to a biocompatible matrix material which may be implanted into the body of the patient for slow sustained release of the reagent. The thrombolytic reagent may also be administered orally or intranasally through the use of nasal sprays containing the reagent.

DETAILED DESCRIPTION OF THE INVENTION

Thrombosis and its complications are considered the most frequent causes of morbidity and death in the adult popu-

lation. The present invention involves a prophylactic method for inhibiting the development of vascular disease such as pulmonary embolus, deep venous thrombus and acute myocardial infarction and cerebral vascular thrombus. The invention relates to the chronic administration of low doses of thrombolytic reagents to prevent vascular disease. The thrombolytic reagents may be administered daily, weekly, monthly or yearly depending on the type of delivery system utilized. The desired goal of any such delivery systems is a constant long term delivery of thrombolytic reagents. Such thrombolytic reagents include, for example, t-PA, streptokinase and urokinase, etc.

The invention is of particular use for treatment of individuals at high risk for vascular disease, such as, diabetics, hypertensive or hyperlipidemia patients, smokers or those individuals with a family history of vascular disease. In such patients, the delivery of a continuous sustained release of thrombolytic reagents, such as t-PA, streptokinase or urokinase, may prevent the development of vascular disease.

Thus, the present invention relates to the chronic administration of low doses of thrombolytic reagents such as tissue plasminogen activator, streptokinase and/or urokinase over prolonged periods of time for prevention of vascular disease. The invention further relates to delivery systems that provide for long-term sustained release of thrombolytic reagents, such as t-PA, in the blood, which is effective as a means for preventing the development of vascular disease. The object of the invention is the prevention or dissolving of clots as they form in the vascular system of the treated patient. In accordance with the present invention, the object can be achieved through the use of t-PA preparations designed for sustained release of t-PA into the bloodstream of a patient over prolonged periods of time.

THROMBOLYTIC REAGENTS

The thrombolytic reagents to be used in the practice of the invention, herein defined as any reagents which have fibrinolytic activity, may be derived from a variety of different sources. For example, the t-PA may be produced in large quantities using recombinant DNA techniques well known to those skilled in the art such as those disclosed in U.S. Pat. No. 4,853,330 which is incorporated herein by reference. Alternatively, the t-PA may be obtained from a number of commercially available sources such as Activase© supplied by Genentech, Inc.

When using t-PA, it is within the scope of the invention that variants of naturally occurring t-PA may also be used in the practice of the invention. In preferred embodiments, such variants of t-PA may have an increased half life or a slower rate of clearance from the body. For example, variants having amino acid substitutions at the proteolytic cleavage sites at position 275, 276 and 277 which render t-PA preparations more stable may be used. Glycosylation mutants at amino acids 117–119, 184–186 and 448–45 exhibit a higher specific activity and such variant may also be used in the practice of the invention. t-PA can also be modified to delete amino acids 51–87 which results in a variant having a slower clearance from plasma. These variants represent only a subset of the known variants of t-PA which may be used in the presently claimed delivery systems.

It is also within the scope of the present invention that thrombolytic reagents other than t-PA may be used in the practice of the invention. Such agents include urokinase and streptokinase both of which may be obtained from commercial sources (Urokinase, Abbott Laboratories; Streptokinase, Pharmacia Adria).

METHOD OF PREVENTING VASCULAR DISEASE

The present invention relates to methods of preventing vascular disease by chronic administration of low doses of thrombolytic reagents. The present invention may be used as a prophylactic means for inhibiting the development of vascular diseases such as cerebral vascular thrombosis, pulmonary embolus, deep venus thrombus and acute myocardial infarction. The invention is of particular use for treatment of individuals at high risk for vascular diseases.

Pharmaceutical compositions suitable for use in the present invention include compositions wherein the thrombolytic ingredients are contained in an effective amount to achieve its intended purpose. More specifically, a therapeutically effective amount means an amount effective to prevent development of vascular disease in the subject being treated. A therapeutically effective dose refers to that amount of the compound that results in plasma levels of the thrombolytic reagent which are sufficient to maintain the beneficial modulating effects. Determination of the effective amounts is well within the capability of those skilled in the art.

The effective dose may be determined using a variety of different assays. For example, assays may be utilized to determine levels of fibrinogen or fibrin split products in the blood of treated patients. In such instances, the effective dose of the thrombolytic reagent is that amount required to sustain normal levels of fibrinogen or fibrin split products in the body of the patient. Such doses may be determined by measuring for levels of fibrinogen (assay for measuring levels of fibrinogen is available from M.L.A.,Inc.) or fibrin split products (Thrombo-Wellco Test;MUREX, Inc.) in the blood of treated patients. A therapeutically effective dose refers to that amount of thrombolytic reagent sufficient to maintain normal circulating blood levels of about 2–4 mg/ml of fibrinogen, or, less than 10 mg/ml of fibrin split products.

The amount of composition administered will, of course, be dependent on the subject being treated, on the subject's weight, the severity of the affliction, the manner of administration and the judgment of the prescribing physician. It should be noted that the attending physician would know how to and when to terminate, interrupt or adjust therapy to lower dosage due to toxicity. Conversely, the attending physician would also know to adjust treatment to higher levels if the clinical response is not adequate (precluding toxicity).

In administering thrombolytic reagents to the patient, it is particularly important to monitor the patient for excessive bleeding or tendencies to bleed. A variety of different diagnostic tests, which are well known to those skilled in the art may be used to access the patients susceptibility to bleeding due to administration of the thrombolytic reagents. Such assays include a complete blood count (CBC), or a determination of prothrombin or partial prothrombin time.

The magnitude of a prophylactic dose of the t-PA in the management of vascular disease will vary with the patient to be treated and the route of administration. Again, it should be noted that the clinician or physician would know when to interrupt and/or adjust the treatment dose due to toxicity. The dose, and perhaps the dosage frequency, will also vary according to the age, body weight, and response of the individual patient.

In general, the total daily dose range of t-PA should be sufficient to achieve serum concentration levels ranging between 1 and 50 mgs. For example, between about 1 and 50 mgs of a daily parenteral dose may be administered, while most preferably a daily dose range should be between

about 10 and 30 mgs of a parenteral dose of t-PA. For smaller patients (less than 65 kg), a dose of 0.1–0.5 mg/kg may be administered daily. It is further recommended that infants, children, and patients over 65 years, and those with impaired renal, or hepatic function, initially receive low doses, and that they be titrated based on individual clinical response(s) and blood level(s). It may be necessary to use dosages outside these ranges in some cases as will be apparent to those of ordinary skill in the art.

THROMBOLYTIC DRUG DELIVERY SYSTEMS

A variety of drug delivery systems may be used to deliver the thrombolytic reagents, such as t-PA into the bloodstream of the patient. For example, the t-PA can be administered to a human patient in pharmaceutical compositions where it is mixed with suitable carriers or excipient(s) at doses therapeutically effective to prevent a variety of vascular disorders. Suitable routes of administration may, for example, include transdermal, topical, oral, intranasal and the like. Dosage forms include but are not limited to aerosol dispersions, creams, patches and the like.

For purposes of clarity, the following discussion describes delivery systems for t-PA. However, the delivery systems are not so limited. It is understood that the delivery systems described below may also be utilized for delivery of other thrombolytic reagents such as urokinase and streptokinase. Techniques for formulation and administration of the thrombolytic reagents of the instant application may be found in "Remington's Pharmaceutical Sciences," Mack Publishing Co., Easton, Pa., latest edition.

Pharmaceutical compositions for use in accordance with the present invention thus may be formulated in conventional manner using one or more physiologically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the t-PA into preparations which can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen. Suitable routes of administration may, for example, include transdermal, topical, oral, intranasal and the like. Dosage forms include but are not limited to aerosol dispersions, creams, patches and the like.

The formulations of the present invention normally will consist of t-PA with a carrier, or diluted by a carrier. Some examples of the diluents or carriers which may be employed in the pharmaceutical compositions of the present invention are lactose, dextrose, sucrose, sorbitol, mannitol, propylene glycol, liquid paraffin, white soft paraffin, kaolin, microcrystalline cellulose, calcium silicate, silica polyvinylpyrrolidone, cetostearyl alcohol, starch, gum acacia, calcium phosphate, cocoa butter, oil of theobroma, arachis oil, alginates, tragacanth, gelatin, syrup B.P., methyl cellulose, polyoxyethylene sorbitan monolaurate, ethyl lactate and propylhydroxybenzoate, sorbitan trioleate, sorbitan sesquioleate and oleyl alcohol.

Because of the short shelf life of t-PA in solution, formulations of t-PA in aqueous solutions, gels, etc. are stored under refrigeration to preserve the activity of the t-PA. Lyophilized preparations of t-PA may be stored at room temperature and protected from excessive exposure to light without loss of activity.

A variety of different drug delivery systems may be used to deliver t-PA into the bloodstream of the patient. In one particular embodiment of the invention a dermal patch may be used for sustained delivery of t-PA into the body. These membrane systems are designed to deliver controlled doses of drugs through the skin into the bloodstream.

TRANSDERMAL DELIVERY SYSTEM

Transdermal delivery of t-PA can be designed so that the rate of delivery of the t-PA closely follows the rate of clearance of the t-PA from the patient's body, thus keeping constant levels of the t-PA in the blood, thereby reducing t-PA waste and overdosing. The use of such a drug delivery system also provides a comfortable, convenient non-invasive method for unattended delivery of t-PA over a prolonged time period.

The transdermal patches to be used in the practice of the invention may be obtained from any of a variety of commercial sources. Most patches consists of a reservoir of drug material located behind a rate controlling membrane. The patch is impregnated with the t-PA and placed on the skin of the patient which allows the drug to penetrate readily into the body. In the practice of the invention the transdermal patch will be periodically replaced as the t-PA becomes depleted.

The transdermal patch is prepared to contain a solution of t-PA. The t-PA is dispersed in the solution, suspension or gel in a dissolved or undissolved state. The drug reservoir of the patch containing a solution, suspension or gel of t-PA also includes permeation enhancers which increase the skin penetration of the t-PA. Such permeation enhancers include those described in U.S. Pat. No. 4,573,966, which is incorporated by reference herein. Permeation enhancers may include plasticizer type enhancers such as lower alky and alkoxy esters of pharmaceutically acceptable fatty acids, fatty acid esters, fatty alcohols and similar hydrophobic compounds that are capable of increasing the permeability of drugs to the skin. In addition, solvent type enhancers may be used to increase the delivery of drugs through the skin. Such enhancers generally refer to relatively hydrophilic compounds having molecular weights of less than 200. More preferably, solvent type enhancers have a molecular weight of less than 150. They are also generally greater than 2 wt % soluble in water, and are preferably greater than 10 wt % soluble in water. Typically, solvent type enhancers include pharmaceutically acceptable lower alkyl alcohol, aryl alcohol, or polyol, for example, ethanol, propanol, butanol, benzyl alcohol, glycerin, or propylene glycol. as well as diluents, such as water or other additives. The solution of t-PA may be formulated to include vascular permeability factors (VPFs), as described in U.S. Pat. No. 5,503,843, which cause a rapid and reversible increase in blood vessel permeability. Such VPF may be added to the t-PA solution to facilitate the uptake of t-PA into the blood vessels of the skin. In addition, gelling agents may be added to increase the viscosity of the solution as is described in U.S. Pat. No. 5,503,843. The t-PA may also include diluents, stabilizers, biocides, antioxidants, anti-irritants and the like.

Because of the instability of t-PA in solution, it is desirable to design transdermal patches that can be stored at room temperature. Such a dermal patch may be designed, for example, with two compartments separated by a breakable barrier; one compartment contains lyophilized t-PA and the other compartment contains a solution or carrier, such as those described above, into which the t-PA is dissolved. Prior to the use of the patch, the barrier is broken, mixing the contents of both compartments thereby forming a drug reservoir containing a solution of t-PA. Alternatively, a transdermal patch may be designed with a single breakable compartment containing lyophilized t-PA, enclosed within the liquid carrier. Prior to use of the patch, the single compartment barrier is broken releasing the lyophilized t-PA into the carrier solution. The patch is then placed in contact with the skin in such a way that the drug reservoir containing the t-PA solution is in contact with the skin.

INTRANASAL DELIVERY SYSTEM

In yet another embodiment of the invention, the t-PA may be administered intranasally. The large blood supply carried in the capillaries of the nose allow drugs to enter the bloodstream quickly. For administration by inhalation, t-PA are conveniently delivered in the form of an aerosol spray

presentation from pressurized packs or a nebulizer, with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of e.g., gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

In addition, the inhalers may be formulated to include vascular permeability factors (VPFs) which cause an increase in blood vessel permeability thereby facilitating the uptake of t-PA into the blood vessels of the nose.

IMPLANTABLE DELIVERY SYSTEMS

In addition to the formulations described above, the t-PA may also be formulated as a slow release preparations that may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the t-PA may be formulated with suitable biocompatible matrix materials. The compounds may be delivered using a sustained-release system, such as slow release gel formations containing the t-PA. Various slow release gel formations have been established and are well known by those skilled in the art. Sustained-release capsules may, depending on their chemical nature, release the t-PA for prolonged periods of time.

ORAL FORMULATIONS

For oral administration, the compounds can be formulated readily by combining the active compounds with pharmaceutically acceptable carriers well known in the art. Such carriers enable the compounds of the invention to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a patient to be treated. Pharmaceutical preparations for oral use can be obtained solid excipient, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, and/or polyvinylpyrrolidone (PVP). If desired, disintegrating agents may be added, such as the cross-linked polyvinyl pyrrolidone, agar, or alginic aced or a salt thereof such as sodium alginate.

Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures.

The t-PA is preferably formulated for oral administration with enteric coatings which protect the t-PA from enzymatic degradation in the stomach and promotes uptake by the intestinal tract. Such formulations are designed for slow release of t-PA through the intestinal wall and into the bloodstream of the patient. For example, the drug capsule containing t-PA may be coated with an enteric film which is sufficiently insoluble at a pH below 7 as to be capable of protecting the capsule and its contents from the digestive enzymes until the capsule reaches a region below the upper part of the intestine. Such film compositions include mixtures of anionic acrylic copolymers derived from at least on monomer selected from acrylic and methacrylic acids and methylacrylates. Such copolymers are commercially available under the trade name "Eudragit"(TM). Such enteric coatings are well known to those skilled in the art, and include those described in U.S. Pat. No. 4910021 and U.S. Pat. No. 5350741, each of which is incorporated by reference herein. Dyestuffs or pigments may also be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

Pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in a mixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added. All formulations for oral administration should be in dosages suitable for such administration.

For buccal administration, the compositions may take the form of tablets or lozenges formulated in a conventional manner.

PARENTERAL FORMULATIONS

The compounds may be formulated for parenteral administration by injection, e.g., by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, e.g., in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulator agents such as suspending, stabilizing and/or dispersing agents.

Pharmaceutical formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form. Additionally, suspensions of the active compounds may be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers or agents which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions.

Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use.

The compounds may also be formulated in rectal compositions such as suppositories or retention enemas, e.g., containing conventional suppository bases such as cocoa butter or other glycerides.

PACKAGING

The compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredient. The pack may for example comprise metal or plastic foil, such as a blister pack. The pack or dispenser device may be accompanied by instructions for administration. Compositions comprising a compound of the invention formulated in a compatible pharmaceutical carrier may also be prepared, placed in an appropriate container, and labelled for treatment of an indicated condition. Suitable conditions indicated on the label may include treatment of patients at risk for development of vascular diseases, or alternatively treatment of patients suffering from vascular diseases such as cerebral vascular

thrombosis, pulmonary embolism, deep venous thrombos, acute myocardial infarction and fresh or aged arterial thrombi.

EXAMPLE

TRANSDERMAL ADMINISTRATION OF THROMBOLYTIC REAGENTS

The following example describes the administration of the thrombolytic reagent t-PA utilizing a transdermal patch delivery system. The use of transdermal patches for the delivery of drugs through the skin is well known. Methods for the use of transdermal patches for delivery of drugs is described, for example, in the following United States patents, U.S Ser. Nos. 5,498,417, 5,503,844 and 5,503,843, each of which is incorporated by reference herein.

The following example illustrates the invention. It is not intended to limit the scope of the invention.

The t-PA (Activase, supplied by GENENTECH, Inc.) to be used in this example is supplied in 50 mg vials. The vials should be reconstituted in either sterile water or a pharmaceutical composition compatible with use in a transdermal patch.

The transdermal patch is prepared to contain a solution of t-PA. The t-PA is dispersed in the solution, suspension or gel in a dissolved or undissolved state. The drug reservoir of the patch containing a solution, suspension or gel of t-PA also includes permeation enhancers which increase the skin penetration of the t-PA. Such permeation enhancers include those described in U.S. Pat. No. 4,573,966, which is incorporated by reference herein. Permeation enhancers may include plasticizer type enhancers such as lower alky and alkoxy esters of pharmaceutically acceptable fatty acids, fatty acid esters, fatty alcohols and similar hydrophobic compounds that are capable of increasing the permeability of drugs to the skin. In addition, solvent type enhancers may be used to increase the delivery of drugs through the skin. Such enhancers generally refer to relatively hydrophilic compounds having molecular weights of less than 200. More preferably, solvent type enhancers have a molecular weight of less than 150. They are also generally greater than 2 wt % soluble in water, and are preferably greater than 10 wt % soluble in water. Typically, solvent type enhancers include pharmaceutically acceptable lower alkyl alcohol, aryl alcohol, or polyol, for example, ethanol, propanol, butanol, benzyl alcohol, glycerin, or propylene glycol. as well as diluents, such as water or other additives. The solution of t-PA may be formulated to include vascular permeability factors (VPFs), as described in U.S. Pat. No. 5503843, which cause a rapid and reversible increase in blood vessel permeability. Such VPF may be added to the t-PA solution to facilitate the uptake of t-PA into the blood vessels of the skin.

The amount of t-PA contained in the patch is that amount necessary to deliver a daily dose of between 1–50 mg of t-PA. The treated patient's blood is monitored to determine the levels of circulating fibrinogen and/or fibrin split products. The amount of t-PA contained in the patch is adjusted so as to maintain blood levels of about 2–4 mg/ml of fibrinogen and 10 mg/ml of fibrin split products. In addition, the treated patient is monitored to prevent excessive bleeding which can result from treatment with thrombolytic reagents.

Once the transdermal patch has been prepared to contain an appropriate dose of t-PA, in a suitable solution, the patients skin is overlaid with the transdermal patch. The patch is placed in contact with the skin in such a way that the side of the patch containing the t-PA solution side is in contact with the patient's skin.

The present invention is not to be limited in scope by the specific embodiments described which are intended as single illustrations of individual aspects of the invention, and functionally equivalent methods and components are within the scope of the invention. Indeed, various modifications of the invention, in addition to those shown and described herein will become apparent to those skilled in the art from the foregoing description and accompanying drawings. Such modifications are intended to fall within the scope of the claims.

What is claimed:

1. A method for prevention of thrombotic vascular disease in a mammal, comprising the chronic administration to a patient in need thereof of an effective dose of a thrombolytic reagent to a mammal.

2. The method of claim 1 wherein the thrombolytic reagent is human tissue plasminogen activator.

3. The method of claim 1 wherein the thrombolytic reagent is streptokinase.

4. The method of claim 1 wherein the thrombolytic reagent is urokinase.

5. The method of claim 1 wherein the thrombolytic reagent is delivered in a transdermal patch.

6. The method of claim 5 wherein the thrombolytic reagent is selected from the group consisting of human tissue plasminogen activator, streptokinase and urokinase.

7. The method of claim 2 wherein the human tissue plasminogen activator is recombinant human tissue plasminogen activator.

8. The method of claim 1 wherein the thrombolytic reagent is delivered intranasally.

9. The method of claim 8 wherein the thrombolytic reagent is selected from the group consisting of human tissue plasminogen activator, streptokinase and urokinase.

10. The method of claim 1 wherein the thrombolytic reagent is delivered topically in a topical cream.

11. The method of claim 10 wherein the thrombolytic reagent is selected from the group consisting of human tissue plasminogen activator, streptokinase and urokinase.

12. The method of claim 1 wherein the thrombolytic reagent is delivered orally.

13. The method of claim 12 wherein the thrombolytic reagent is selected from the group consisting of human tissue plasminogen activator, streptokinase and urokinase.

14. The method of claim 1 wherein the dose of the thrombolytic reagent is that dose sufficient to maintain circulating blood levels of 2–4 mg/ml of fibrinogen or less than 10 mg/ml of fibrin split products.

15. The method of claim 1 wherein the dose of the thrombolytic reagent is that dose sufficient to maintain circulating blood levels of less than 10 mg/ml of fibrin split products.

16. The method of claim 2 wherein the daily dose of t-PA is between 1–50 mg.

17. The method of claim 2 wherein the daily dose of t-PA is between 10–30 mg.

* * * * *

EXHIBIT B

AJH 2004; 17:823–827

Effect of Amlodipine–Atorvastatin Combination on Fibrinolysis in Hypertensive Hypercholesterolemic Patients With Insulin Resistance

Roberto Fogari, Giuseppe Derosa, Pierangelo Lazzari, Annalisa Zoppi, Elena Fogari, Andrea Rinaldi, and Amedeo Mugellini

Background: The aim of this study was to evaluate the effect of the amlodipine–atorvastatin combination on plasma tissue plasminogen activator (t-PA) and plasminogen activator inhibitor type 1 (PAI-1) activity in hypercholesterolemic, hypertensive patients with insulin resistance.

Methods: The study population included 45 patients, aged 41 to 70 years, with mild to moderate essential hypertension (diastolic blood pressure [BP] ≥95 and ≤105 mm Hg), hypercholesterolemia (total cholesterol >200 and <350 mg/dL), and insulin resistance (HOMA index >2.5) After a 4-week wash-out period, they were randomized to amlodipine (5 mg) or atorvastatin (20 mg) or their combination at the same oral dosage for 12 weeks in three cross-over periods each separated by a 4-week placebo period (3 by 3 latin square design). At the end of the placebo wash-out and of each treatment period, office BP, total cholesterol, PAI-1, and t-PA activity were evaluated.

Results: The amlodipine–atorvastatin combination, in addition to the expected hypocholesterolemic effect, produced: 1) a greater decrease in PAI-1 activity (−10.2 U/mL, $P < .01$ *v* placebo) and an even greater increase in t-PA activity (+0.26 U/mL, $P < .01$ *v* placebo) than amlodipine (−0.5 U/mL for PAI-1, P = not significant; +0.17 U/mL for t-PA, $P < .01$ *v* placebo) and atorvastatin alone (respectively, −9.9 U/mL, $P < .01$ *v* placebo and +0.08 U/mL, $P < .05$ *v* placebo); and 2) a greater systolic BP/diastolic BP mean reduction (−22/17 mm Hg, $P < .005$ *v* placebo) than amlodipine (−18/14 mm Hg, $P < .01$ *v* placebo) and atorvastatin alone (−2.8/3.8 mm Hg, $P < .05$ *v* placebo only for diastolic BP).

Conclusions: The positive effect on fibrinolytic balance and BP control observed suggests that in hypertensive, hypercholesterolemic patients with impaired fibrinolysis, the combination of amlodipine and atorvastatin could be the treatment of choice. Am J Hypertens 2004;17:823–827 © 2004 American Journal of Hypertension, Ltd.

Key Words: Amlodipine, atorvastatin, fibrinolysis, hypertension, hypercholesterolemia.

Population-based data have indicated that the two most common cardiovascular risk factors, hypertension and hypercholesterolemia, coexist in a large proportion of patients and their combination is associated with a rate of cardiovascular complications that greatly exceeds the separate contribution of any single risk factor.[1,2] In hypertension, a close relationship has also been demonstrated between disorders of lipid metabolism, insulin resistance, and impaired fibrinolysis, mainly expressed as increased plasminogen activator inhibitor type 1 (PAI-1) levels and depressed tissue plasminogen activator (t-PA) activity.[3–5] Endothelial dysfunction might be the pathogenetic link between these risk factors whose clustering greatly accelerates the atherogenic process and its clinical complications.[6] To achieve a reduction in both cardiovascular morbidity and mortality, current hypertension treatment guidelines stress the role of total risk factor management and state not only to lower blood pressure (BP) values but also to normalize high cholesterol and improve the global risk profile of hypertensive patients.[6]

The 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitors, commonly referred to as statins,

Received January 30, 2004. First decision April 5, 2004. Accepted June 4, 2004.

From the Department of Internal Medicine and Therapeutics, Clinica Medica II IRCCS Policlinico S.Matteo, University of Pavia, Pavia, Italy.

Address correspondence and reprint requests to Dr. Roberto Fogari, Clinica Medica II, piazzale Golgi 2, 27100 Pavia, Italy; e-mail: r.fogari@smatteo.pv.it

0895-7061/04/$30.00
doi:10.1016/j.amjhyper.2004.06.005

are the most powerful agents available for the treatment of patients with hypercholesterolemia. Statins have demonstrated a capability to reduce the rate of cardiovascular events.[7–9] Data from the recent Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) support the view that statins protect hypertensive patients from end-organ damage, not only through cholesterol reduction but also through other pathways.[10] These include a direct modulation of the endothelial function, as well as an interaction with the fibrinolytic activity.[11,12] In this regard, evidence from in vitro studies indicate that statins positively affect the fibrinolytic system of cultured smooth muscle cells as well as endothelial cells.[13–15] Also some in vivo studies demonstrated that statins decreased PAI-1 plasma levels and increased t-PA activity.[16,17] Whether statin treatment may affect fibrinolytic activity has been poorly investigated in hypercholesterolemic, hypertensive patients pharmachologically treated for both risk factors.

Given this background, the present study was undertaken to evaluate the effect of the combination of the dihydropyridine calcium antagonist amlodipine and the HMG-CoA reductase inhibitor atorvastatin on plasma PAI-1 and t-PA activity in hypercholesterolemic, hypertensive patients with insulin resistance, a condition characterized by impaired fibrinolysis.[18]

Methods

The study population was selected according to the following inclusion criteria: outpatients of either sex, aged 56.3 ± 5.1 years, with mild to moderate essential hypertension (diastolic BP >90 and ≤105 mm Hg), total cholesterol (TC) >200 and <350 mg/dL, and insulin resistance, as defined by HOmeostasis Model Assessment (HOMA) Index >2.5. The HOMA Index (= glucose in millimoles per liter × insulin in microunits per milliliter/22.5) has been shown to correlate well with insulin resistance using clamp techniques.[19]

Patients with a diagnosis of diabetes, liver or kidney disease, cancer, major cardiovascular complication (myocardial infarction or unstable angina within 6 months, congestive heart failure), using corticosteroids or hormone replacement therapies, and having any other diseases with a poor prognosis were exluded from the study. Secondary forms of hypertension were excluded according to standard routine clinical and laboratory examination. The study protocol was approved by the local Ethical Committee and informed consent was obtained from each participant at the time of enrollment.

After an initial 4-week wash-out period, patients were randomly assigned to receive amlodipine (5 mg) or atorvastatin (20 mg) or their combination at the same oral dosage for 12 weeks in three cross-over periods each separated by a 4-week placebo wash-out period (3 by 3 latin square). At the end of the placebo wash-out and of each treatment period, office BP, TC, HDL cholesterol, LDL cholesterol, triglycerides, plasma PAI-1, and t-PA activity were evaluated. The BP measurements were obtained from each patient in the seated position using a standard mercury sphygmomanometer (Korotkoff I and V). Measurements were taken in the morning before daily drug intake (ie, 24 h after dosing) and after the subject had rested 10 min in a quiet room. Three successive BP readings were obtained at 1-min intervals and averaged. For evaluation of lipid and fibrinolytic parameters, blood was always drawn in the morning, between 8 and 9 AM, after a 15-min rest and after an overnight fast, to reduce interference by the diurnal variation of the PAI-1 and tPA.[20] The TC and TG were determined by the enzymatic method of the Chemetron Company (Frankfurt, Germany). The HDL cholesterol was determined by the enzymatic method of Roschlau[21] after LDL and very low-density lipoprotein (VLDL) precipitation with polyethylene glycol 6000 by the method of Viikari.[22] The LDL cholesterol was calculated by the formula of Friedewald et al.[23]

For fibrinolytic measurements, blood samples were collected in Biopool stabilyte tubes with citrate buffer, at pH 4.5, to ensure the stability of t-PA activity without affecting the assay of PAI-1 activity. Plasma was separated within 1 h by centrifugation for 20 min at 3000 *g* and stored at −70°C until assay. Plasma t-PA activity was determined with a parabolic rate assay based on fibrin stimulation of the t-PA-catalyzed conversion of Glu-plasminogen to plasmin, which subsequently cleaves the chromogenic substrate.[24] The t-PA activity was expressed in international units per milliliter by reference to the World Health Organization First International Standard for t-PA coded 86/670 from the National Institutes for Biological Standard and Control, Potters Bar, England. Plasma PAI-1 activity was determined with a two-stage, indirect enzymatic assay based on the addition of excess t-PA (40 UI) to the samples and measurement of the residual t-PA activity.[25] One unit of PAI-1 activity was defined as the amount of PAI-1 that inhibits 1 UI of international t-PA standard. The reagent kits for assay of t-PA and PAI-1 activities were purchased from Biopool AB, Umea, Sweden. The coefficients of variation for repeated measures of PAI-1 activity and t-PA activity in our laboratory were 5% and 8.5%, respectively.

Data are expressed as mean ± standard deviation. The statistical analysis was conducted by using SAS version 8 (SAS Institute Inc., Cary, NC). Analysis of variance (ANOVA) for the cross-over design (general linear model procedure) was used to analyze the results. Statistical significance was set at $P < .05$. To verify the basic of the crossover design,[26] the possibility of a carry-over or sequence effect was also investigated using the crossover ANOVA test.

Results

Forty-five patients, 22 men and 23 women, aged 41 to 70 years, were enrolled in the study and 41 patients completed it. Four patients dropped out, one because of side effects and three for lack of cooperation.

Table 1. Effect of each treatment on blood pressure, lipids, and fibrinolytic parameters

	Baseline	Atorvastatin 20 mg	Amlodipine 5 mg	Amlodipine + Atorvastatin
SBP (mm Hg)	158.3 ± 11.1	155.5 ± 11.2	140.3 ± 9.9†	136.1 ± 9.9‡
DBP (mm Hg)	96.1 ± 4.5	92.3 ± 4.4*	81.8 ± 4.1†	78.4 ± 4.2‡
TC (mg/dL)	264.3 ± 18.2	187.2 ± 14.3†	251.6 ± 16.9	180.5 ± 13.9†
HDL-C (mg/dL)	42.9 ± 5.1	46.2 ± 4.3*	43.1 ± 4.8	46.8 ± 4.1*
LDL-C (mg/dL)	193.5 ± 15.3	119.6 ± 11.6†	186.8 ± 15.2	111.6 ± 11.5†
TG (mg/dL)	139.3 ± 39	113.1 ± 33	134.2 ± 40	110.5 ± 34
PAI-1 (U/mL)	23.1 ± 11.3	13.2 ± 6.7*	22.6 ± 11.2	12.9 ± 6.8*
t-PA (U/mL)	0.51 ± 0.22	0.59 ± 0.14*	0.68 ± 0.20†	0.77 ± 0.25§

DBP = diastolic blood pressure; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; PAI-1 = plasminogen activator inhibitor type 1; SBP = systolic blood pressure; TC = total cholesterol; TG = triglycerides; t-PA = tissue plasminogen activator.

Values expressed as mean ± standard deviation.

* $P < .05$ *v* placebo; † $P < .01$ *v* placebo; ‡ $P < .005$ *v* placebo; § $P < .05$ *v* amlodipine.

The main results of the study are reported in Table 1. As expected, amlodipine monotherapy was significantly effective in reducing both systolic BP (−18 mm Hg, −11.3%, $P < .01$ *v* placebo) and diastolic BP mean values (−14.3 mm Hg, −14.8%, $P < .01$ *v* placebo). Treatment with atorvastatin alone did not affect systolic BP values (−2.8 mm Hg, −1.7%, P = not significant), whereas it significantly reduced diastolic BP values (−3.8 mm Hg, −3.9%, $P < .05$ *v* placebo), although to a lesser extent compared with amlodipine. Interestingly, combination therapy with amlodipine plus atorvastatin produced a significantly greater reduction in both systolic BP (−22.2 mm Hg, −14%, $P < .005$ *v* placebo) and diastolic BP mean values (−17 mm Hg, −18.4%, $P < .005$ *v* placebo) than either drug alone.

Amlodipine monotherapy did not modify the lipid profile of the treated patients, whereas atorvastatin significantly reduced TC (−77.1 mg/dL, −29.1%, $P < .01$ *v* placebo) and LDL cholesterol levels (−73.9 mg/dL, −38.1%, $P < .01$ *v* placebo) and increased HDL cholesterol (+3.3 mg/dL, +7.6%, $P < .05$ *v* placebo), without affecting TG levels. Adding amlodipine did not significantly modify the lipid-lowering effect of atorvastatin.

Treatment with amlodipine alone did not affect plasma PAI-1 activity (−0.5 U/mL, −2.1%, P = not significant), whereas significantly increased t-PA activity (+0.17 u/mL, +33.3%, $P < .01$ *v* placebo). Atorvastatin monotherapy significantly decreased PAI-1 activity (−9.9 U/mL, −42.8%, $P < .01$ *v* placebo) and increased t-PA activity (+0.08 U/mL, +16.6%, $P < .05$ *v* placebo). The amlodipine–atorvastatin combination produced a significantly greater reduction in PAI-1 activity (−10.2 U/mL, −44.1%, $P < .01$ *v* placebo) and an even greater increase in t-PA activity (+0.26 U/mL, +50.9%, $P < .01$ *v* placebo and $P < .05$ *v* amlodipine) than either drug alone. No relationship was find between the changes in plasma PAI-1 and t-PA activity and the hypocholesterolemic effect or the BP lowering produced by the amlodipine–atorvastatin combination.

Discussion

The results of this study showed that in hypercholesterolemic, hypertensive patients with impaired fibrinolysis, the amlodipine–atorvastatin combination, beyond the expected hypocholesterolemic effect: 1) improved the fibrinolytic balance by decreasing the PAI-1 activity and particularly by increasing t-PA activity more than the single monotherapies; and 2) decreased both systolic and diastolic BP levels more than either drug alone.

The most original findings of our study were those regarding the effects of the amlodipine–atorvastatin combination on the fibrinolytic system. In agreement with some previous observations,[27] amlodipine monotherapy did not modify PAI-1 activity, whereas it significantly increased t-PA activity. Mechanisms for such an effect are unknown, although a direct action of amlodipine on vascular endothelium is likely to play an important role. Amlodipine has been suggested to improve endothelial function, mainly through an antioxidant action.[28,29] Because both PAI-1 and t-PA are synthetized in the vascular endothelium and endothelial dysfunction induces an imbalance in fibrinolysis,[30,31] improving endothelial function might reverse the fibrinolytic imbalance.

The results obtained with atorvastatin monotherapy (ie, a significant decrease in PAI-1 activity and an increase in t-PA activity) confirm the findings of some in vitro and in vivo studies.[13–17] Statins have been shown to reduce PAI-1 production in cultured human endothelial and smooth muscle cells and to increase t-PA production in human smooth muscle cells.[13] In addition, they increased fibrinolytic activity in tumor necrosis factor-α-activated human peritoneal mesothelial cells[15] and downregulated the synthesis of PAI-1 in cultured human monocytes.[14] Although the results of in vivo studies are more controversial, in some studies statins decreased plasma PAI-1 and increased t-PA activity.[14,15] The mechanism by which statins inhibit PAI-1 and increase t-PA expression appears

to be directly associated with geranylgeranylation of some cell proteins.[12,14,32,33]

Interestingly, in the present study the combination of amlodipine and atorvastatin improved the fibrinolytic balance more than the single monotherapy. In particular, a greater decrease in PAI-1 activity (−44%) and even a greater increase in t-PA activity (+51%) were observed. These results, which were independent from the changes in TC and BP levels induced by the amlodipine–atorvastatin combination, could be related to an additive effect of the two drugs at the endothelial level.

This study also demonstrated that the use of atorvastatin in addition to amlodipine in patients with hypertension and high cholesterol levels not only improved the lipid profile by reducing TC and LDL cholesterol and increasing HDL cholesterol levels, but also significantly improved BP control. This effect, which confirms previous observations of a positive interaction between statins and antihypertensive agents,[34,35] seems to be independent from the reduction in plasma cholesterol values and suggests the possibility of a positive synergistic interaction between atorvastatin and amlodipine. The rationale for such clinical synergism could involve a direct BP-lowering effect of statins, possibly related to an improvement of endothelium-mediated vasorelaxation and to reduced arterial stiffness and vasoconstriction.[15,36] Atorvastatin has been demonstrated to reduce BP in untreated hypertensive patients independently of its cholesterol-lowering effect[33,37] and also in the present study, atorvastatin monotherapy produced a significant reduction in diastolic BP values. Statins also seem capable of improving the sensitivity of the vessel wall to the vasodilating effect of antihypertensive drugs. Statins have been demonstrated to improve endothelium-dependent vascular function and cause a significant vasodilation.[38] This could result in a significant increase in the sensitivity of the vessel wall to the vasodilating action of amlodipine. Some retrospective analyses investigating the extent of the interaction between statins and different classes of antihypertensive drugs have shown that the effect on BP control was enhanced in patients who were given statins in combination with angiotensin-converting enzyme inhibitors and calcium channel blockers, whereas no significant interactions were observed with the use of β-blockers and diuretics.[3] The enhanced interaction between statins and drugs acting mainly at the level of the vascular wall (angiotensin-converting enzyme inhibitor and calcium channel blocker) support the hypothesis that treatment with statins may enhance the capability of some classes of drugs to reduce the peripheral tone and to improve the peripheral vasodilator capacity.[35]

From a clinical point of view, the additional BP reduction and the increased fibrinolytic activity observed by combining amlodipine and atorvastatin could significantly contribute to reducing the global cardiovascular risk in hypertensive, hypercholesterolemic patients and improve the overall preventive action of antihypertensive and lipid-lowering therapy. Such additional properties deserve further research.

In conclusion, the positive effect exerted by the amlodipine–atorvastatin combination on fibrinolytic balance and BP control, beyond its cholesterol-lowering effect, suggest that this combination could be the treatment of choice in hypertensive patients with hypercholesterolemia and impaired fibrinolysis.

References

1. Kannel WB: Risk stratification in hypertension: new insights from the Framingham Study. Am J Hypertens 2000;13(Suppl)3S–10S.
2. Borghi C: Interactions between hypercholesterolemia and hypertension: implications for therapy. Curr Opin Nephrol Hypertens 2002; 11:489–496.
3. Landin K, Tengborn L, Smith U: Elevated fibrinogen and plasminogen activator inhibitor (PAI-1) in hypertension are related to metabolic risk factors for cardiovascular disease. J Intern Med 1990; 227:273–278.
4. Jeng JR, Sheu WH, Jeng CY, Huang SH, Shieh SM: Impaired fibrinolysis and insulin resistance in patients with hypertension. Am J Hypertens 1996;9:484–490.
5. Tomijama H, Kimura Y, Mitsuhashi H, Kinouchi T, Yoshida H, Kushiro T, Doba N: Relationship between endothelial function and fibrinolysis in early hypertension. Hypertension 1998;31:321–327.
6. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, Oparil S, Wright JT Jr, Roccella EJ: The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. The JNC VII Report. JAMA 2003;289:2569–2572.
7. The Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) Study Group: Prevention of cardiovascular events and deaths with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. N Engl J.Med 1998;339: 1349–1357.
8. Byington RP, Davis BR, Plehn JF, White HD, Baker J, Cobbe SM, Shepherd J: Reduction of stroke events with pravastatin: the Prospective Pravastatin Pooling (PPP) project. Circulation 2001;103: 387–392.
9. Schwartz GG, Olsson AG, Ezekowitz MD, Ganz P, Oliver MF, Waters D, Zeiher A, Chaitman BR, Leslie S, Stern T: Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes. The MIRACL Study: a randomized controlled trial. JAMA 2001;285:1711–1718.
10. Sever PS, Dahlof B, Poulter NR, Wedel H, Beevers G, Caulfield M, Collins R, Kjeldsen SE, Kristinsson A, McInnes GT: Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower than average cholesterol concentrations in the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA): a multicenter randomised controlled trial. Lancet 2003;361:1149–1158.
11. Takemoto M, Liao JK: Pleiotropic effects of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors. Arterioscler Thromb Vasc Biol 2001;21:1712–1719.
12. Wolfrum S, Jensen K, Liao JK: Endothelium-dependent effects of statins. Arterioscler Thromb Vasc Biol 2003;23:729–736.
13. Wiesbauer F, Kaun C, Zorn G, Maurer G, Huber K, Wojta J: HMG CoA reductase inhibitors affect the fibrinolytic system in human vascular cells in vitro: a comparative study using different statins. Br J Pharmacol 2002;135:284–292.
14. Ishibashi T, Nagata K, Ohkawara H, Sakamoto T, Yokoyama K, Shindo J, Sugimoto K, Sakuruda S, Takuwa Y, Teramoto T, Maruyama Y: Inhibition of Rho/Rho-kinase signaling downregulates plasminogen activator inhibitor-1 synthesis in cultured human monocytes. Biochim Biophys Acta 2002;1590:123–130.

15. Haslinger B, Kleemann R, Toet KH, Kooistra T: Simvastatin suppresses tissue factor expression and increases fibrinolytic activity in tumor necrosis factor-alpha-activated human peritoneal mesothelial cells. Kidney Int 2003;63:2065–2074.
16. Bevilacqua M, Bettica P, Milani M, Vago T, Rogolino A, Righini V, Santoli E, Norbiato G: Effect of fluvastatin on lipids and fibrinolysis in coronary artery disease. Am J Cardiol 1997;79:84–87.
17. Seljeflot I, Tonstad S, Hjermann I, Arnesen H: Improved fibrinolysis after 1-year treatment with HMG CoA reductase inhibitors in patients with coronary heart disease. Thromb Res 2002;105:285–290.
18. Vague Ph, Juhan-Vague I, Ailhoud MF, Badoer Ch, Viard M, Collen D: Correlation between blood fibrinolytic activity, plasminogen activator inhibitor level, plasma insulin level and relative body weight in normal and obese subjects. Metabolism 1986;35:250–263.
19. Lansang MC, Williams GH, Carrol J: Correlation between the glucose clamp technique and the homeostasis model assessment in hypertension. Am J Hypertens 2001;14:51–53.
20. Kluft C, Jie AFH, Rijken DC, Verheijen JH: Daytime fluctuations in blood of tissue-type plasminogen activator (tPA) and its fasting inhibitor (PAI-1). Thromb Haemost 1989;59:329–332.
21. Roschlau P: Enzymatische bestimmung des gesamtcholesterin in serum. Z Klin Chem Klin Biochem 1974;12:403.
22. Viikari J: Precipitation of plasma lipoproteins by PEG-6000 and its evaluation with electrophoresis and ultracentrifugation. Scand J Clin Lab Invest 1976;36:265–271.
23. Friedewald WT, Levy RI, Fredrickson DS: Estimation of the concentration of low density lipoprotein cholesterol in plasma without use of the preparative ultracentrifuge. Clin Chem 1972;18:499–502.
24. Wiman B, Mellbring G, Randy M: Plasminogen activator release during venous stasis and exercise as determined by a new specific assay. Clin Chim Acta 1983;127:279–288.
25. Chmielewska J, Randy M, Wiman B: Evidence for a rapid inhibitor to tissue plasminogen activator in plasma. Thromb Res 1983;31:427–436.
26. Senn SJ: Crossover Trials in Clinical Research. New York, John Wiley, 1993, pp 38–46.
27. Gleerup G, Winther K: Decreased fibrinolytic activity and increased platelet function in hypertension. Am J Hypertens 1991;4:168S–171S.
28. Ghiadoni L, Magagna A, Versari D, Kardasa I, Huang Y, Taddei S, Salvetti A: Different effect of antihypertensive drugs on artery endothelial function. Hypertension 2003;41:1281–1286.
29. Mason RPO: Atheroprotective effects of long-acting dihydropyridine-type calcium channel blockers: evidence from clinical trials and basic scientific research. Cerebrovasc Dis 2003;16(Suppl):11–17.
30. Lijnen HR, Collen D: Endothelium in hemostasis and thrombosis. Prog Cardiovasc Dis 1993;22(Suppl 4):81–S14.
31. Rubanyi GM: The role of endothelium in cardiovascular homeostasis and diseases. J Cardiovasc Pharmacol 1993,22(Suppl 4):S1–S14.
32. Essig M, Nguyen G, Prie D, Escoubet B, Sraer JD, Friedlander G. 3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibitors increase fibrinolytic activity in rat aortic endothelial cells: role of geranylgeranylation and Rho proteins. Circ Res 1998;83:683–690.
33. Swiatkowska M, Pawlowska Z, Szemraj J, Drzewoski J, Wataja C, Cerniewski CS: Cerivastatin,a HMG-CoA reductase inhibitor, reduces plasminogen activator inhibitor-1 (PAI-1) expression in endothelial cells by down-regulation of cellular signaling and inhibition of PAI-1 promoter activity. Jpn J Pharmacol 2002;90:337–344.
34. Sposito AC, Mansur AP, Coelho OR, Nicolau JC, Ramires JA: Additional reduction in blood pressure after cholesterol lowering treatment by statins (lovastatin or pravastatin) in hypercholesterolemic patients using angiotensin converting enzyme inhibitors (enalapril or lisinopril). Am J Cardiol 1999;83:1497–1499.
35. Borghi C, Dormi A, Veronesi M, Immordino V, Ambrosioni E: Use of lipid lowering drugs and blood pressure control in patients with arterial hypertension. J Clin Hypertens 2002;4:277–285.
36. Ferrier KR, Muhlmann MH, Baguet JP, Cameron JD, Jennings GL, Dart AM, Kingwell BA: Intensive cholesterol reduction lowers blood pressure and large artery stiffness in isolated systolic hypertension. J Am Coll Cardiol 2002;39:1020–1025.
37. Glorioso N, Troffa C, Filigheddu F, Dettori F, Soro A, Parpaglia PP, Collatina S, Pahor M: Effect of the HMG-CoA reductase inhibitors on blood pressure in patients with essential hypertension and primary hypercholesterolemia. Hypertension 1999;34:1281–1286.
38. Kaesemyer WH, Caldwell RB, Huang J, Caldwell RW: Pravastatin sodium activates endothelial nitric oxide synthase independent of its cholesterol lowering actions. J Am Coll Cardiol 1999;33:234–241.

EXHIBIT C

Licensing & Development
Pfizer Inc
235 East 42nd Street
Tel 212 573 1995 Fax 212 573 3684
Email ann.barry@pfizer.com

Ann C. Barry, Ph.D.
Director

September 14, 2005

Eugene Berman
The Rotbert Law Group
111 Rockville Pike
Suite 400
Rockville, MD 20850

Dear Mr. Berman,

Your letter of August 5th to our Chairman, Hank McKinnell, regarding U.S. Patent No. 5,837,688 was referred to me since I reside in Pfizer's Licensing and Development Group and have responsibility for Cardiovascular Products.

The above mentioned patent covers the fibnrinolytic activity of numerous cardiovascular products and your proposal suggests that the patent may have relevance to Lipitor (atorvastatin calcium). Your proposal was therefore reviewed by a number of Pfizer individuals representing the cardiovascular scientific/medical discipline as well as from an IP perspective.

Lipitor has no indications that are dependent upon anti-thrombotic or fibrinolytic activity and there is no plan to pursue such an indication. The Pfizer team therefore concluded that the patent would have minimal value to Pfizer and that there was no interest in further discussing this licensing opportunity.

We thank you for offering this opportunity to Pfizer and we wish you well with the initiative.

Best regards,

Ann

cc: Alan Hesketh

EXHIBIT C

February 25, 2008 02:21 PM Eastern Daylight Time

Pfizer Voluntarily Withdraws Lipitor Advertising Featuring Dr. Robert Jarvik

Company Commits to Ensuring Greater Clarity Regarding Spokespeople

NEW YORK–(BUSINESS WIRE)–Pfizer said today that it is voluntarily withdrawing Lipitor advertising and promotion featuring Dr. Robert Jarvik and committing to ensuring greater clarity in the roles and responsibilities of its spokespeople in its consumer advertising and promotion.

Commenting on the withdrawal of the Jarvik advertising and promotion, Pfizer's President of Worldwide Pharmaceutical Operations Ian Read said:

"The consumer advertising featuring Dr. Jarvik, a well-respected heart expert and inventor of the Jarvik artificial heart, provided valuable and medically accurate information about the risks of high cholesterol and how Lipitor can help patients reduce their risk of heart attack and stroke. Direct-to-consumer advertising is an important way to provide consumers with information about their health and treating disease, and at least 29 million Americans have talked to their physicians about a health condition for the first time after seeing a pharmaceutical advertisement.

"Nevertheless, the way in which we presented Dr. Jarvik in these ads has, unfortunately, led to misimpressions and distractions from our primary goal of encouraging patient and physician dialogue on the leading cause of death in the world – cardiovascular disease. We regret this. Going forward, we commit to ensuring there is greater clarity in our advertising regarding the presentation of spokespeople.

"Raising awareness of the dangers of cardiovascular disease in the U.S. remains an urgent public health priority. Only half of all Americans who have high LDL cholesterol are even diagnosed, and just half of those are being treated. Future Lipitor campaigns, to be launched in several weeks, will continue to stress the critical importance of patients talking to their doctors so they can make informed choices about their treatment options," he added.

The benefits of statins such as Lipitor in treating heart disease are validated in clinical guidelines including those from the National Institutes of Health National Cholesterol Education Program, the American Heart Association, the American College of Cardiology and the American Diabetes Association. Lipitor has an established safety profile across the full dose range which is based on more than 15 years of clinical trial experience and nearly 144 million patient-years of experience.

Important US Prescribing Information

Lipitor is a prescription medication. It is used in patients with multiple risk factors for heart disease such as family history, high blood pressure, age, low HDL ("good" cholesterol) or smoking to reduce the risk of a heart attack and stroke, certain kinds of heart surgery and chest pain.

Lipitor is also used in patients with type 2 diabetes and at least one other risk factor for heart disease such as high blood pressure, smoking or complications of diabetes, including eye disease and protein in urine, to reduce the risk of heart attack and stroke.

Lipitor is used in patients with existing coronary heart disease to reduce the risk of heart attack, stroke, certain kinds of heart surgery, hospitalization for heart failure, and chest pain.

When diet and exercise alone are not enough, Lipitor is used along with a low-fat diet and exercise to lower cholesterol.

Print

Lipitor is not for everyone. It is not for those with liver problems. And it is not for women who are nursing, pregnant or may become pregnant.

Patients taking Lipitor should tell their doctors if they feel any new muscle pain or weakness. This could be a sign of rare but serious muscle side effects. Patients should tell their doctors about all medications they take. This may help avoid serious drug interactions. Doctors should do blood tests to check liver function before and during treatment and may adjust the dose. The most common side effects are gas, constipation, stomach pain and heartburn. They tend to be mild and often go away.

For additional product information, visit www.Lipitor.com.

Contacts

Pfizer Inc
Vanessa Aristide, 212-733-3784
Ray Kerins, 212-733-9203

BusinessWire

EXHIBIT D

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-702/S-039

Pfizer Inc., US Agent for
Pfizer Ireland Pharmaceuticals
Attention: Madeleine M. Jester
Director, US Regulatory Affairs
235 East 42nd Street
New York, NY 10017

Dear Ms. Jester:

Please refer to your supplemental new drug application dated September 30, 2003, received October 1, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lipitor (Atorvastatin calcium) tablets.

We acknowledge receipt of your submissions dated July 16, 26, 28 (email), and 30 (email), 2004.

This supplemental New Drug Application provides for new indications, based on the results of the Anglo-Scandinavian Cardiovascular Outcomes Trial Lipid Lowering Arm (ASCOT-LLA), for the use of atorvastatin in adult patients without clinically evident coronary heart disease (but with multiple risk factors for coronary heart disease such as age $\geq$ 55 years, smoking, hypertension, low HDL-C or a family history of early coronary heart disease), to reduce the risk of myocardial infarction, and to reduce the risk for revascularization procedures and angina. In addition, this supplemental application provides for changes to the CLINICAL PHARMACOLOGY, INDICATIONS AND USAGE and ADVERSE EVENTS sections of the LIPITOR package insert.

We completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

We note your commitment to submit the full study report for ASCOT, the parent trial for ASCOT-LLA, within one year of completion or termination of ASCOT.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert submitted July 30, 2004)(copy enclosed).

Please submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – NDAs*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20-702/S-039." Approval of this submission by FDA is not required before the labeling is used.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are waiving the pediatric study requirement for this application.

In addition, submit three copies of the introductory promotional materials that you propose to use for product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Margaret Simoneau, M.S. R.Ph., Regulatory Project Manager, at (301) 827-6411.

Sincerely,

{See appended electronic signature page}

David G. Orloff, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Eric Colman
7/30/04 11:55:44 AM
Eric Colman for David Orloff

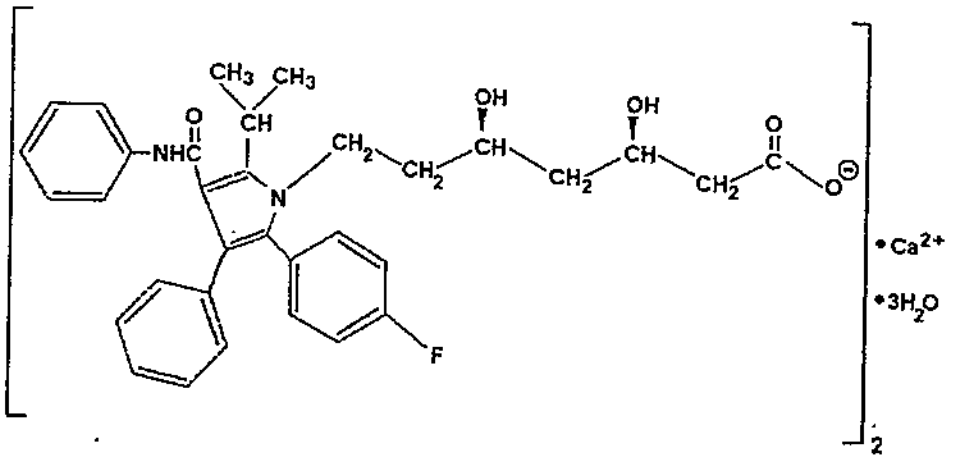
EXHIBIT E

Lipitor®
(Atorvastatin Calcium)
Tablets

DESCRIPTION

LIPITOR® (atorvastatin calcium) is a synthetic lipid-lowering agent. Atorvastatin is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in cholesterol biosynthesis.

Atorvastatin calcium is [R-(R*, R*)]-2-(4-fluorophenyl)-ß, δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino) carbonyl]-1H-pyrrole-1-heptanoic acid, calcium salt (2:1) trihydrate. The empirical formula of atorvastatin calcium is $(C_{33}H_{34}FN_2O_5)_2Ca \cdot 3H_2O$ and its molecular weight is 1209.42. Its structural formula is:



Atorvastatin calcium is a white to off-white crystalline powder that is insoluble in aqueous solutions of pH 4 and below. Atorvastatin calcium is very slightly soluble in distilled water, pH 7.4 phosphate buffer, and acetonitrile, slightly soluble in ethanol, and freely soluble in methanol.

LIPITOR tablets for oral administration contain 10, 20, 40 or 80 mg atorvastatin and the following inactive ingredients: calcium carbonate, USP; candelilla wax, FCC; croscarmellose sodium, NF; hydroxypropyl cellulose, NF; lactose monohydrate, NF; magnesium stearate, NF; microcrystalline cellulose, NF; Opadry White YS-1-7040 (hypromellose, polyethylene glycol, talc, titanium dioxide); polysorbate 80, NF; simethicone emulsion.

CLINICAL PHARMACOLOGY

Mechanism of Action

Atorvastatin is a selective, competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methylglutaryl-coenzyme A to mevalonate, a precursor of sterols, including cholesterol. Cholesterol and triglycerides circulate in the bloodstream as part of lipoprotein complexes. With ultracentrifugation, these complexes separate into HDL (high-density lipoprotein), IDL (intermediate-density lipoprotein), LDL (low-density lipoprotein), and VLDL (very-low-density lipoprotein) fractions. Triglycerides (TG) and cholesterol in the liver are incorporated into VLDL and released into the plasma for delivery to peripheral tissues. LDL is formed from VLDL and is catabolized primarily through the high-affinity LDL receptor. Clinical and pathologic studies show that elevated plasma levels of total cholesterol (total-C), LDL-cholesterol (LDL-C), and apolipoprotein B (apo B) promote human atherosclerosis and are risk factors for developing cardiovascular disease, while increased levels of HDL-C are associated with a decreased cardiovascular risk.

In animal models, LIPITOR lowers plasma cholesterol and lipoprotein levels by inhibiting HMG-CoA reductase and cholesterol synthesis in the liver and by increasing the number of hepatic LDL receptors on the cell-surface to enhance uptake and catabolism of LDL; LIPITOR also reduces LDL production and the number of LDL particles. LIPITOR reduces LDL-C in some patients with homozygous familial hypercholesterolemia (FH), a population that rarely responds to other lipid-lowering medication(s).

A variety of clinical studies have demonstrated that elevated levels of total-C, LDL-C, and apo B (a membrane complex for LDL-C) promote human atherosclerosis. Similarly, decreased levels of HDL-C (and its transport complex, apo A) are associated with the development of atherosclerosis. Epidemiologic investigations have established that cardiovascular morbidity and mortality vary directly with the level of total-C and LDL-C, and inversely with the level of HDL-C.

LIPITOR reduces total-C, LDL-C, and apo B in patients with homozygous and heterozygous FH, nonfamilial forms of hypercholesterolemia, and mixed dyslipidemia. LIPITOR also reduces VLDL-C and TG and produces variable increases in HDL-C and apolipoprotein A-1. LIPITOR reduces total-C, LDL-C, VLDL-C, apo B, TG, and non-HDL-C, and increases HDL-C in patients with isolated hypertriglyceridemia. LIPITOR reduces intermediate density lipoprotein cholesterol (IDL-C) in patients with dysbetalipoproteinemia.

Like LDL, cholesterol-enriched triglyceride-rich lipoproteins, including VLDL, intermediate density lipoprotein (IDL), and remnants, can also promote atherosclerosis. Elevated plasma triglycerides are frequently found in a triad with low HDL-C levels and small LDL particles, as well as in association with non-lipid metabolic risk factors for

coronary heart disease. As such, total plasma TG has not consistently been shown to be an independent risk factor for CHD. Furthermore, the independent effect of raising HDL or lowering TG on the risk of coronary and cardiovascular morbidity and mortality has not been determined.

Pharmacodynamics

Atorvastatin as well as some of its metabolites are pharmacologically active in humans. The liver is the primary site of action and the principal site of cholesterol synthesis and LDL clearance. Drug dosage rather than systemic drug concentration correlates better with LDL-C reduction. Individualization of drug dosage should be based on therapeutic response (see DOSAGE AND ADMINISTRATION).

Pharmacokinetics and Drug Metabolism

Absorption: Atorvastatin is rapidly absorbed after oral administration; maximum plasma concentrations occur within 1 to 2 hours. Extent of absorption increases in proportion to atorvastatin dose. The absolute bioavailability of atorvastatin (parent drug) is approximately 14% and the systemic availability of HMG-CoA reductase inhibitory activity is approximately 30%. The low systemic availability is attributed to presystemic clearance in gastrointestinal mucosa and/or hepatic first-pass metabolism. Although food decreases the rate and extent of drug absorption by approximately 25% and 9%, respectively, as assessed by Cmax and AUC, LDL-C reduction is similar whether atorvastatin is given with or without food. Plasma atorvastatin concentrations are lower (approximately 30% for Cmax and AUC) following evening drug administration compared with morning. However, LDL-C reduction is the same regardless of the time of day of drug administration (see DOSAGE AND ADMINISTRATION).

Distribution: Mean volume of distribution of atorvastatin is approximately 381 liters. Atorvastatin is ≥98% bound to plasma proteins. A blood/plasma ratio of approximately 0.25 indicates poor drug penetration into red blood cells. Based on observations in rats, atorvastatin is likely to be secreted in human milk (see CONTRAINDICATIONS, Pregnancy and Lactation, and PRECAUTIONS, Nursing Mothers).

Metabolism: Atorvastatin is extensively metabolized to ortho- and parahydroxylated derivatives and various beta-oxidation products. *In vitro* inhibition of HMG-CoA reductase by ortho- and parahydroxylated metabolites is equivalent to that of atorvastatin. Approximately 70% of circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites. *In vitro* studies suggest the importance of atorvastatin metabolism by cytochrome P450 3A4, consistent with increased plasma concentrations of atorvastatin in humans following coadministration with erythromycin, a known inhibitor of this isozyme (see PRECAUTIONS, Drug Interactions). In animals, the ortho-hydroxy metabolite undergoes further glucuronidation.

Excretion: Atorvastatin and its metabolites are eliminated primarily in bile following hepatic and/or extra-hepatic metabolism; however, the drug does not appear to undergo

enterohepatic recirculation. Mean plasma elimination half-life of atorvastatin in humans is approximately 14 hours, but the half-life of inhibitory activity for HMG-CoA reductase is 20 to 30 hours due to the contribution of active metabolites. Less than 2% of a dose of atorvastatin is recovered in urine following oral administration.

Special Populations

Geriatric: Plasma concentrations of atorvastatin are higher (approximately 40% for Cmax and 30% for AUC) in healthy elderly subjects (age ≥65 years) than in young adults. Clinical data suggest a greater degree of LDL-lowering at any dose of drug in the elderly patient population compared to younger adults (see PRECAUTIONS section; Geriatric Use subsection).

Pediatric: Pharmacokinetic data in the pediatric population are not available.

Gender: Plasma concentrations of atorvastatin in women differ from those in men (approximately 20% higher for Cmax and 10% lower for AUC); however, there is no clinically significant difference in LDL-C reduction with LIPITOR between men and women.

Renal Insufficiency: Renal disease has no influence on the plasma concentrations or LDL-C reduction of atorvastatin; thus, dose adjustment in patients with renal dysfunction is not necessary (see DOSAGE AND ADMINISTRATION).

Hemodialysis: While studies have not been conducted in patients with end-stage renal disease, hemodialysis is not expected to significantly enhance clearance of atorvastatin since the drug is extensively bound to plasma proteins.

Hepatic Insufficiency: In patients with chronic alcoholic liver disease, plasma concentrations of atorvastatin are markedly increased. Cmax and AUC are each 4-fold greater in patients with Childs-Pugh A disease. Cmax and AUC are approximately 16-fold and 11-fold increased, respectively, in patients with Childs-Pugh B disease (see CONTRAINDICATIONS).

Clinical Studies

Prevention of Cardiovascular Disease

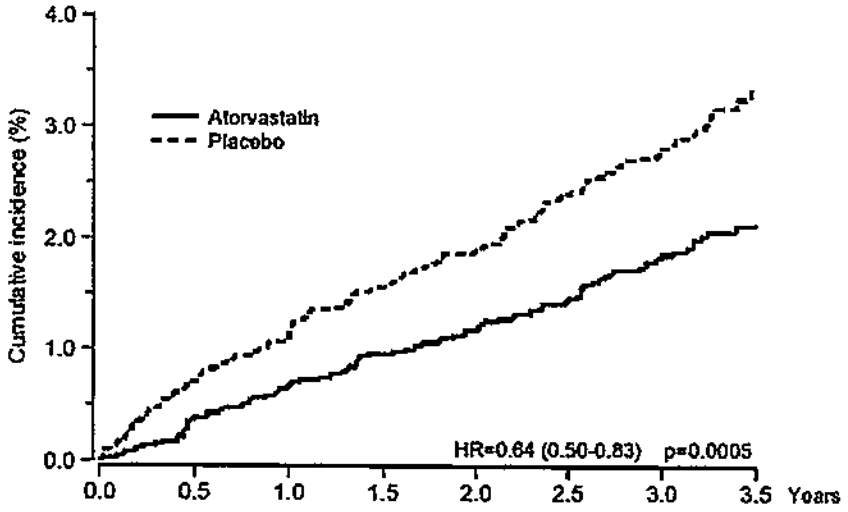
In the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), the effect of LIPITOR (atorvastatin calcium) on fatal and non-fatal coronary heart disease was assessed in 10,305 hypertensive patients 40-80 years of age (mean of 63 years), without a previous myocardial infarction and with TC levels ≤251 mg/dl (6.5 mmol/l). Additionally all patients had at least 3 of the following cardiovascular risk factors: male gender (81.1%), age >55 years (84.5%), smoking (33.2%), diabetes (24.3%), history of CHD in a first-degree relative (26%), TC:HDL >6 (14.3%), peripheral vascular disease (5.1%), left ventricular hypertrophy (14.4%), prior cerebrovascular event (9.8%), specific ECG

abnormality (14.3%), proteinuria/albuminuria (62.4%). In this double-blind, placebo-controlled study patients were treated with anti-hypertensive therapy (Goal BP <140/90 mm Hg for non-diabetic patients, <130/80 mm Hg for diabetic patients) and allocated to either LIPITOR 10 mg daily (n=5168) or placebo (n=5137), using a covariate adaptive method which took into account the distribution of nine baseline characteristics of patients already enrolled and minimized the imbalance of those characteristics across the groups. Patients were followed for a median duration of 3.3 years.

The effect of 10 mg/day of LIPITOR on lipid levels was similar to that seen in previous clinical trials.

LIPITOR significantly reduced the rate of coronary events [either fatal coronary heart disease (46 events in the placebo group vs. 40 events in the LIPITOR group) or nonfatal MI (108 events in the placebo group vs. 60 events in the LIPITOR group)] with a relative risk reduction of 36% [(based on incidences of 1.9% for LIPITOR vs. 3.0% for placebo), p=0.0005 (see Figure 1)]. The risk reduction was consistent regardless of age, smoking status, obesity or presence of renal dysfunction. The effect of LIPITOR was seen regardless of baseline LDL levels. Due to the small number of events, results for women were inconclusive.

Figure 1: Effect of LIPITOR 10 mg/day on Cumulative Incidence of Nonfatal Myocardial Infarction or Coronary Heart Disease Death (in ASCOT-LLA)



LIPITOR also significantly decreased the relative risk for revascularization procedures by 42%. Although the reduction of fatal and non-fatal strokes did not reach a pre-defined significance level (p=0.01), a favorable trend was observed with a 26% relative risk reduction (incidences of 1.7% for LIPITOR and 2.3% for placebo). There was no significant difference between the treatment groups for death due to cardiovascular causes (p=0.51) or noncardiovascular causes (p=0.17).

In the Collaborative Atorvastatin Diabetes Study (CARDS), the effect of LIPITOR (atorvastatin calcium) on cardiovascular disease (CVD) endpoints was assessed in 2838

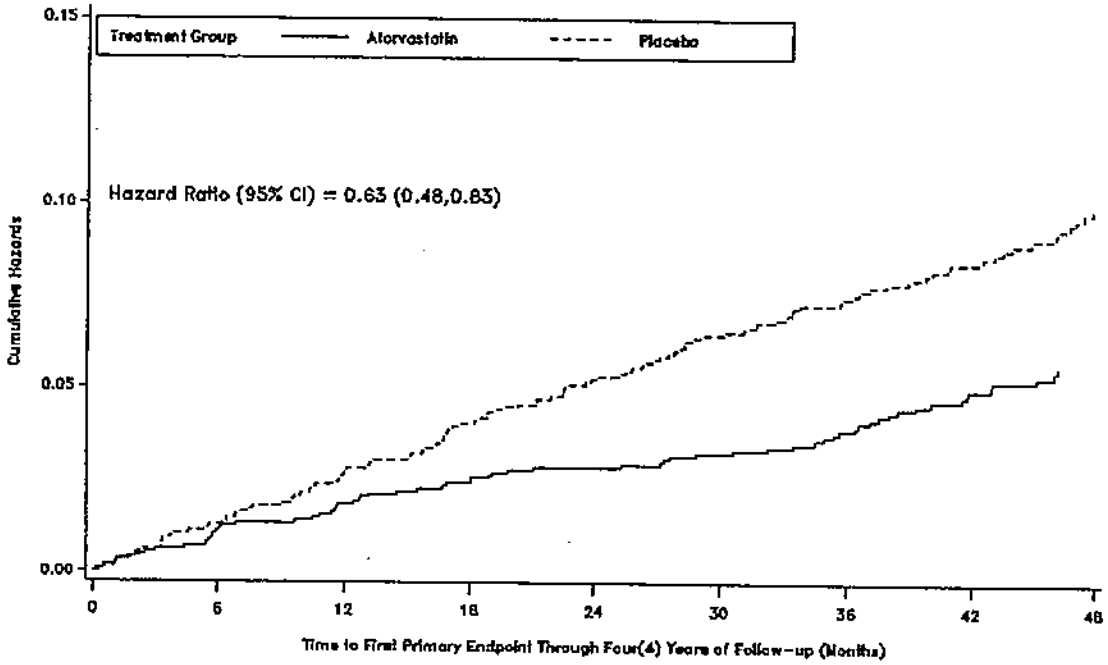
subjects (94% White, 68% male), ages 40-75 with type 2 diabetes based on WHO criteria, without prior history of cardiovascular disease and with LDL≤ 160 mg/dL and TG ≤600 mg/dL. In addition to diabetes, subjects had 1 or more of the following risk factors: current smoking (23%), hypertension (80%), retinopathy (30%), or microalbuminuria (9%) or macroalbuminuria (3%). No subjects on hemodialysis were enrolled in the study. In this multicenter, placebo-controlled, double-blind clinical trial, subjects were randomly allocated to either LIPITOR 10 mg daily (1429) or placebo (1411) in a 1:1 ratio and were followed for a median duration of 3.9 years. The primary endpoint was the occurrence of any of the major cardiovascular events: myocardial infarction, acute CHD death, unstable angina, coronary revascularization, or stroke. The primary analysis was the time to first occurrence of the primary endpoint.

Baseline characteristics of subjects were: mean age of 62 years, mean HbA_{1c} 7.7%; median LDL-C 120 mg/dL; median TC 207 mg/dL; median TG 151 mg/dL; median HDL-C 52mg/dL.

The effect of LIPITOR 10 mg/ day on lipid levels was similar to that seen in previous clinical trials.

LIPITOR significantly reduced the rate of major cardiovascular events (primary endpoint events) (83 events in the LIPITOR group vs. 127 events in the placebo group) with a relative risk reduction of 37%, HR 0.63, 95% CI (0.48,0.83) (p=0.001) (see Figure 2). An effect of LIPITOR was seen regardless of age, sex, or baseline lipid levels.

Figure 2. Effect of LIPITOR 10 mg/day on Time to Occurrence of Major Cardiovascular Event (myocardial infarction, acute CHD death, unstable angina, coronary revascularization, or stroke) in CARDS.



LIPITOR significantly reduced the risk of stroke by 48% (21 events in the LIPITOR group vs 39 events in the placebo group), HR 0.52, 95% CI (0.31,0.89) (p=0.016) and reduced the risk of MI by 42% (38 events in the LIPITOR group vs 64 events in the placebo group), HR 0.58, 95.1% CI (0.39, 0.86) (p=0.007). There was no significant difference between the treatment groups for angina, revascularization procedures, and acute CHD death.

There were 61 deaths in the LIPITOR group vs 82 deaths in the placebo group, (HR 0.73, p=0.059).

In the Treating to New Targets Study (TNT), the effect of LIPITOR 80 mg/day vs. LIPITOR 10 mg/day on the reduction in cardiovascular events was assessed in 10,001 subjects (94% white, 81% male, 38% ≥65 years) with clinically evident coronary heart disease who had achieved a target LDL-C level <130 mg/dL after completing an 8-week, open-label, run-in period with LIPITOR 10 mg/day. Subjects were randomly assigned to either 10 mg/day or 80 mg/day of LIPITOR and followed for a median duration of 4.9 years. The primary endpoint was the time-to-first occurrence of any of the following major cardiovascular events (MCVE): death due to CHD, non-fatal myocardial infarction, resuscitated cardiac arrest, and fatal and non-fatal stroke. The mean LDL-C,

TC, TG, non-HDL and HDL cholesterol levels at 12 weeks were 73, 145, 128, 98 and 47 mg/dL during treatment with 80 mg of LIPITOR and 99, 177, 152, 129 and 48 mg/dL during treatment with 10 mg of LIPITOR.

Treatment with LIPITOR 80 mg/day significantly reduced the rate of MCVE (434 events in the 80mg/day group vs 548 events in the 10 mg/day group) with a relative risk reduction of 22%, HR 0.78, 95% CI (0.69,0.89), p=0.0002 (see Figure 3 and Table 1). The overall risk reduction was consistent regardless of age (<65, ≥65) or gender.

Figure 3. Effect of LIPITOR 80 mg/day vs.10 mg/day on Time to Occurrence of Major Cardiovascular Events (TNT)

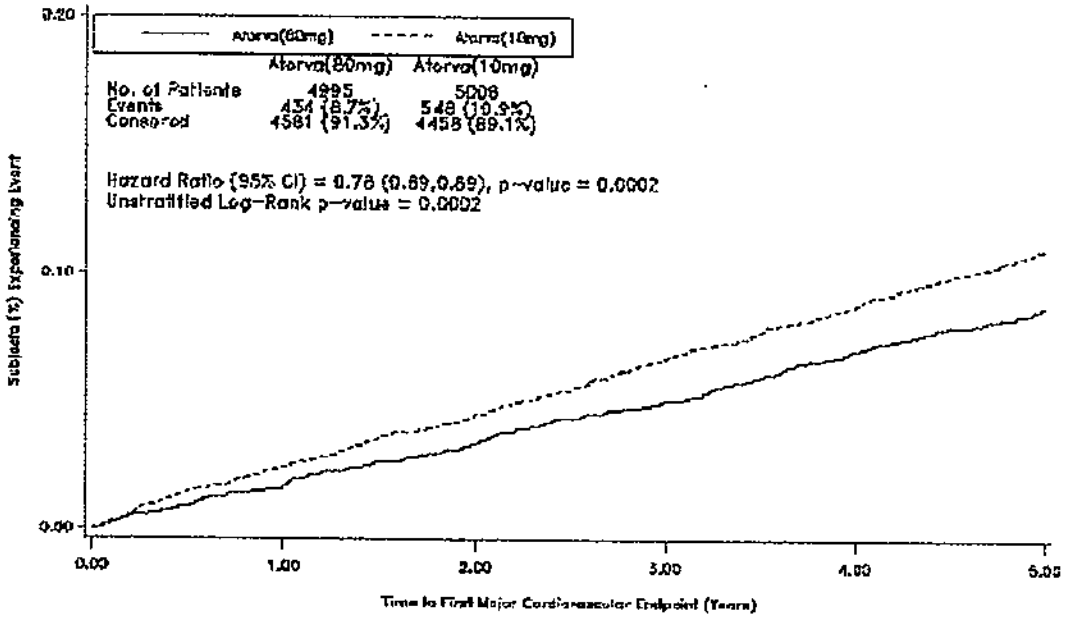


TABLE 1. Overview of Efficacy Results in TNT

Endpoint	Atorvastatin 10 mg (N=5006)		Atorvastatin 80 mg (N=4995)		HR[a] (95%CI)
PRIMARY ENDPOINT	n	(%)	n	(%)	
First major cardiovascular endpoint	548	(10.9)	434	(8.7)	0.78 (0.69, 0.89)
Components of the Primary Endpoint					
CHD death	127	(2.5)	101	(2.0)	0.80 (0.61, 1.03)
Nonfatal, non-procedure related MI	308	(6.2)	243	(4.9)	0.78 (0.66, 0.93)
Resuscitated cardiac arrest	26	(0.5)	25	(0.5)	0.96 (0.56, 1.67)
Stroke (fatal and non-fatal)	155	(3.1)	117	(2.3)	0.75 (0.59, 0.96)
SECONDARY ENDPOINTS*					
First CHF with hospitalization	164	(3.3)	122	(2.4)	0.74 (0.59, 0.94)
First PVD endpoint	282	(5.6)	275	(5.5)	0.97 (0.83, 1.15)
First CABG or other coronary revascularization procedure[b]	904	(18.1)	667	(13.4)	0.72 (0.65, 0.80)
First documented angina endpoint[b]	615	(12.3)	545	(10.9)	0.88 (0.79, 0.99)
All cause mortality	282	(5.6)	284	(5.7)	1.01 (0.85, 1.19)
Components of all cause mortality					
Cardiovascular death	155	(3.1)	126	(2.5)	0.81 (0.64, 1.03)
Noncardiovascular death	127	(2.5)	158	(3.2)	1.25 (0.99, 1.57)
Cancer death	75	(1.5)	85	(1.7)	1.13 (0.83, 1.55)
Other non-CV death	43	(0.9)	58	(1.2)	1.35 (0.91, 2.00)
Suicide, homicide and other traumatic non-CV death	9	(0.2)	15	(0.3)	1.67 (0.73, 3.82)

a Atorvastatin 80 mg: atorvastatin 10 mg
b component of other secondary endpoints
* secondary endpoints not included in primary endpoint
HR=hazard ratio; CHD=coronary heart disease; CI=confidence interval; MI=myocardial infarction; CHF=congestive heart failure; CV=cardiovascular; PVD=peripheral vascular disease; CABG=coronary artery bypass graft
Confidence intervals for the Secondary Endpoints were not adjusted for multiple comparisons

Of the events that comprised the primary efficacy endpoint, treatment with LIPITOR 80 mg/day significantly reduced the rate of nonfatal, non-procedure related MI and fatal and non-fatal stroke, but not CHD death or resuscitated cardiac arrest (Table 1). Of the predefined secondary endpoints, treatment with LIPITOR 80 mg/day significantly reduced the rate of coronary revascularization, angina and hospitalization for heart failure, but not peripheral vascular disease. The reduction in the rate of CHF with hospitalization was only observed in the 8% of patients with a prior history of CHF.

There was no significant difference between the treatment groups for all-cause mortality (Table 1). The proportions of subjects who experienced cardiovascular death, including the components of CHD death and fatal stroke were numerically smaller in the LIPITOR 80 mg group than in the LIPITOR 10 mg treatment group. The proportions of subjects who experienced noncardiovascular death were numerically larger in the LIPITOR 80 mg group than in the LIPITOR 10 mg treatment group.

In the Incremental Decrease in Endpoints Through Aggressive Lipid Lowering Study (IDEAL), treatment with LIPITOR 80 mg/day was compared to treatment with simvastatin 20-40 mg/day in 8,888 subjects up to 80 years of age with a history of CHD to assess whether reduction in CV risk could be achieved. Patients were mainly male (81%), white (99%) with an average age of 61.7 years, and an average

LDL-C of 121.5 mg/dL at randomization; 76% were on statin therapy. In this prospective, randomized, open-label, blinded endpoint (PROBE) trial with no run-in period, subjects were followed for a median duration of 4.8 years. The mean LDL-C, TC, TG, HDL and non-HDL cholesterol levels at Week 12 were 78, 145, 115, 45 and 100 mg/dL during treatment with 80 mg of LIPITOR and 105, 179, 142, 47 and 132 mg/dL during treatment with 20-40 mg of simvastatin.

There was no significant difference between the treatment groups for the primary endpoint, the rate of first major coronary event (fatal CHD, nonfatal MI and resuscitated cardiac arrest): 411 (9.3%) in the LIPITOR 80 mg/day group vs. 463 (10.4%) in the simvastatin 20-40 mg/day group, HR 0.89, 95% CI (0.78,1.01), p=0.07.

There were no significant differences between the treatment groups for all-cause mortality: 366 (8.2%) in the LIPITOR 80 mg/day group vs. 374 (8.4%) in the simvastatin 20-40 mg/day group. The proportions of subjects who experienced CV or non-CV death were similar for the LIPITOR 80 mg group and the simvastatin 20-40 mg group.

Hypercholesterolemia (Heterozygous Familial and Nonfamilial) and Mixed Dyslipidemia *(Fredrickson* Types IIa and IIb)

LIPITOR reduces total-C, LDL-C, VLDL-C, apo B, and TG, and increases HDL-C in patients with hypercholesterolemia and mixed dyslipidemia. Therapeutic response is seen within 2 weeks, and maximum response is usually achieved within 4 weeks and maintained during chronic therapy.

LIPITOR is effective in a wide variety of patient populations with hypercholesterolemia, with and without hypertriglyceridemia, in men and women, and in the elderly. Experience in pediatric patients has been limited to patients with homozygous FH. In two multicenter, placebo-controlled, dose-response studies in patients with hypercholesterolemia, LIPITOR given as a single dose over 6 weeks significantly reduced total-C, LDL-C, apo B, and TG (Pooled results are provided in Table 1).

TABLE 2. Dose-Response in Patients With Primary Hypercholesterolemia (Adjusted Mean % Change From Baseline)[a]

Dose	N	TC	LDL-C	Apo B	TG	HDL-C	Non-HDL-C/ HDL-C
Placebo	21	4	4	3	10	-3	7
10	22	-29	-39	-32	-19	6	-34
20	20	-33	-43	-35	-26	9	-41
40	21	-37	-50	-42	-29	6	-45
80	23	-45	-60	-50	-37	5	-53

[a] Results are pooled from 2 dose-response studies.

In patients with *Fredrickson* Types IIa and IIb hyperlipoproteinemia pooled from 24 controlled trials, the median (25th and 75th percentile) percent changes from baseline in HDL-C for atorvastatin 10, 20, 40, and 80 mg were 6.4 (-1.4, 14), 8.7(0, 17), 7.8(0, 16),

and 5.1 (-2.7, 15), respectively. Additionally, analysis of the pooled data demonstrated consistent and significant decreases in total-C, LDL-C, TG, total-C/HDL-C, and LDL-C/HDL-C.

In three multicenter, double-blind studies in patients with hypercholesterolemia, LIPITOR was compared to other HMG-CoA reductase inhibitors. After randomization, patients were treated for 16 weeks with either LIPITOR 10 mg per day or a fixed dose of the comparative agent (Table 3).

TABLE 3. Mean Percent Change From Baseline at Endpoint (Double-Blind, Randomized, Active-Controlled Trials)

Treatment (Daily Dose)	N	Total-C	LDL-C	Apo B	TG	HDL-C	Non-HDL-C/ HDL-C
Study 1							
Atorvastatin 10 mg	707	-27[a]	-36[a]	-28[a]	-17[a]	+7	-37[a]
Lovastatin 20 mg	191	-19	-27	-20	- 6	+7	-28
95% CI for Diff[1]		-9.2, -6.5	-10.7, -7.1	-10.0, -6.5	-15.2, -7.1	-1.7, 2.0	-11.1, -7.1
Study 2							
Atorvastatin 10 mg	222	-25[b]	-35[b]	-27[b]	-17[b]	+6	-36[b]
Pravastatin 20 mg	77	-17	-23	-17	- 9	+8	-28
95% CI for Diff[1]		-10.8, -6.1	-14.5, -8.2	-13.4, -7.4	-14.1, -0.7	-4.9, 1.6	-11.5, -4.1
Study 3							
Atorvastatin 10 mg	132	-29[c]	-37[c]	-34[c]	-23[c]	+7	-39[c]
Simvastatin 10 mg	45	-24	-30	-30	-15	+7	-33
95% CI for Diff[1]		-8.7, -2.7	-10.1, -2.6	-8.0, -1.1	-15.1, -0.7	-4.3, 3.9	-9.6, -1.9

[1] A negative value for the 95% CI for the difference between treatments favors atorvastatin for all except HDL-C, for which a positive value favors atorvastatin. If the range does not include 0, this indicates a statistically significant difference.

[a] Significantly different from lovastatin, ANCOVA, $p \leq 0.05$

[b] Significantly different from pravastatin, ANCOVA, $p \leq 0.05$

[c] Significantly different from simvastatin, ANCOVA, $p \leq 0.05$

The impact on clinical outcomes of the differences in lipid-altering effects between treatments shown in Table 3 is not known. Table 3 does not contain data comparing the effects of atorvastatin 10 mg and higher doses of lovastatin, pravastatin, and simvastatin. The drugs compared in the studies summarized in the table are not necessarily interchangeable.

Hypertriglyceridemia *(Fredrickson* Type IV)

The response to LIPITOR in 64 patients with isolated hypertriglyceridemia treated across several clinical trials is shown in the table below. For the atorvastatin-treated patients, median (min, max) baseline TG level was 565 (267-1502).

TABLE 4. Combined Patients With Isolated Elevated TG: Median (min, max) Percent Changes From Baseline

	Placebo (N=12)	Atorvastatin 10 mg (N=37)	Atorvastatin 20 mg (N=13)	Atorvastatin 80 mg (N=14)
Triglycerides	-12.4 (-36.6, 82.7)	-41.0 (-76.2, 49.4)	-38.7 (-62.7, 29.5)	-51.8 (-82.8, 41.3)
Total-C	-2.3 (-15.5, 24.4)	-28.2 (-44.9, -6.8)	-34.9 (-49.6, -15.2)	-44.4 (-63.5, -3.8)
LDL-C	3.6 (-31.3, 31.6)	-26.5 (-57.7, 9.8)	-30.4 (-53.9, 0.3)	-40.5 (-60.6, -13.8)
HDL-C	3.8 (-18.6, 13.4)	13.8 (-9.7, 61.5)	11.0 (-3.2, 25.2)	7.5 (-10.8, 37.2)
VLDL-C	-1.0 (-31.9, 53.2)	-48.8 (-85.8, 57.3)	-44.6 (-62.2, -10.8)	-62.0 (-88.2, 37.6)
non-HDL-C	-2.8 (-17.6, 30.0)	-33.0 (-52.1, -13.3)	-42.7 (-53.7, -17.4)	-51.5 (-72.9, -4.3)

Dysbetalipoproteinemia *(Fredrickson* Type III)

The results of an open-label crossover study of 16 patients (genotypes: 14 apo E2/E2 and 2 apo E3/E2) with dysbetalipoproteinemia *(Fredrickson* Type III) are shown in the table below.

TABLE 5. Open-Label Crossover Study of 16 Patients With Dysbetalipoproteinemia (*Fredrickson* Type III)

	Median (min, max) at Baseline (mg/dL)	Median % Change (min, max)	
		Atorvastatin 10 mg	Atorvastatin 80 mg
Total-C	442 (225, 1320)	-37 (-85, 17)	-58 (-90, -31)
Triglycerides	678 (273, 5990)	-39 (-92, -8)	-53 (-95, -30)
IDL-C + VLDL-C	215 (111, 613)	-32 (-76, 9)	-63 (-90, -8)
non-HDL-C	411 (218, 1272)	-43 (-87, -19)	-64 (-92, -36)

Homozygous Familial Hypercholesterolemia

In a study without a concurrent control group, 29 patients ages 6 to 37 years with homozygous FH received maximum daily doses of 20 to 80 mg of LIPITOR. The mean LDL-C reduction in this study was 18%. Twenty-five patients with a reduction in LDL-C had a mean response of 20% (range of 7% to 53%, median of 24%); the remaining 4 patients had 7% to 24% increases in LDL-C. Five of the 29 patients had absent LDL-receptor function. Of these, 2 patients also had a portacaval shunt and had no significant reduction in LDL-C. The remaining 3 receptor-negative patients had a mean LDL-C reduction of 22%.

Heterozygous Familial Hypercholesterolemia in Pediatric Patients

In a double-blind, placebo-controlled study followed by an open-label phase, 187 boys and postmenarchal girls 10-17 years of age (mean age 14.1 years) with heterozygous familial hypercholesterolemia (FH) or severe hypercholesterolemia were randomized to LIPITOR (n=140) or placebo (n=47) for 26 weeks and then all received LIPITOR for 26 weeks. Inclusion in the study required 1) a baseline LDL-C level ≥ 190 mg/dL or 2) a

baseline LDL-C ≥ 160 mg/dL and positive family history of FH or documented premature cardiovascular disease in a first- or second-degree relative. The mean baseline LDL-C value was 218.6 mg/dL (range: 138.5-385.0 mg/dL) in the LIPITOR group compared to 230.0 mg/dL (range: 160.0-324.5 mg/dL) in the placebo group. The dosage of LIPITOR (once daily) was 10 mg for the first 4 weeks and up-titrated to 20 mg if the LDL-C level was > 130 mg/dL. The number of LIPITOR-treated patients who required up-titration to 20 mg after Week 4 during the double-blind phase was 80 (57.1%).

LIPITOR significantly decreased plasma levels of total-C, LDL-C, triglycerides, and apolipoprotein B during the 26 week double-blind phase (see Table 6).

TABLE 6
Lipid-altering Effects of LIPITOR in Adolescent Boys and Girls with Heterozygous Familial Hypercholesterolemia or Severe Hypercholesterolemia
(Mean Percent Change from Baseline at Endpoint in Intention-to-Treat Population)

DOSAGE	N	Total-C	LDL-C	HDL-C	TG	Apolipoprotein B
Placebo	47	-1.5	-0.4	-1.9	1.0	0.7
LIPITOR	140	-31.4	-39.6	2.8	-12.0	-34.0

The mean achieved LDL-C value was 130.7 mg/dL (range: 70.0-242.0 mg/dL) in the LIPITOR group compared to 228.5 mg/dL (range: 152.0-385.0 mg/dL) in the placebo group during the 26 week double-blind phase.

The safety and efficacy of doses above 20 mg have not been studied in controlled trials in children. The long-term efficacy of LIPITOR therapy in childhood to reduce morbidity and mortality in adulthood has not been established.

INDICATIONS AND USAGE

Prevention of Cardiovascular Disease

In adult patients without clinically evident coronary heart disease, but with multiple risk factors for coronary heart disease such as age, smoking, hypertension, low HDL-C, or a family history of early coronary heart disease, LIPITOR is indicated to:

- Reduce the risk of myocardial infarction
- Reduce the risk of stroke
- Reduce the risk for revascularization procedures and angina

In patients with type 2 diabetes, and without clinically evident coronary heart disease, but with multiple risk factors for coronary heart disease such as retinopathy, albuminuria, smoking, or hypertension, LIPITOR is indicated to:

- Reduce the risk of myocardial infarction
- Reduce the risk of stroke

In patients with clinically evident coronary heart disease, LIPITOR is indicated to:

- Reduce the risk of non-fatal myocardial infarction
- Reduce the risk of fatal and non-fatal stroke

- Reduce the risk for revascularization procedures
- Reduce the risk of hospitalization for CHF
- Reduce the risk of angina

Hypercholesterolemia
LIPITOR is indicated:

1. as an adjunct to diet to reduce elevated total-C, LDL-C, apo B, and TG levels and to increase HDL-C in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia *(Fredrickson* Types IIa and IIb);

2. as an adjunct to diet for the treatment of patients with elevated serum TG levels*(Fredrickson* Type IV);

3. for the treatment of patients with primary dysbetalipoproteinemia *(Fredrickson* Type III) who do not respond adequately to diet;

4. to reduce total-C and LDL-C in patients with homozygous familial hypercholesterolemia as an adjunct to other lipid-lowering treatments (eg, LDL apheresis) or if such treatments are unavailable;

5. as an adjunct to diet to reduce total-C, LDL-C, and apo B levels in boys and postmenarchal girls, 10 to 17 years of age, with heterozygous familial hypercholesterolemia if after an adequate trial of diet therapy the following findings are present:

   a. LDL-C remains ≥ 190 mg/dL or
   b. LDL-C remains ≥ 160 mg/dL and:
      - there is a positive family history of premature cardiovascular disease or
      - two or more other CVD risk factors are present in the pediatric patient

Therapy with lipid-altering agents should be a component of multiple-risk-factor intervention in individuals at increased risk for atherosclerotic vascular disease due to hypercholesterolemia. Lipid-altering agents should be used in addition to a diet restricted in saturated fat and cholesterol only when the response to diet and other nonpharmacological measures has been inadequate (see *National Cholesterol Education Program (NCEP) Guidelines,* summarized in Table 7).

TABLE 7. NCEP Treatment Guidelines: LDL-C Goals and Cutpoints for Therapeutic Lifestyle Changes and Drug Therapy in Different Risk Categories

Risk Category	LDL-C Goal (mg/dL)	LDL Level at Which to Initiate Therapeutic Lifestyle Changes (mg/dL)	LDL Level at Which to Consider Drug Therapy (mg/dL)
CHD [a] or CHD risk equivalents (10-year risk >20%)	<100	≥100	≥130 (100-129: drug optional) [b]

2+ Risk Factors (10-year risk ≤20%)	<130	≥130	10-year risk 10%-20%: ≥130 10-year risk <10%: ≥ 160
0-1 Risk factor [c]	<160	≥160	≥190 (160-189: LDL-lowering drug optional)

[a] CHD, coronary heart disease

[b] Some authorities recommend use of LDL-lowering drugs in this category if an LDL-C level of < 100 mg/dL cannot be achieved by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and HDL-C, e.g., nicotinic acid or fibrate. Clinical judgement also may call for deferring drug therapy in this subcategory.

[c] Almost all people with 0-1 risk factor have 10-year risk <10%; thus, 10-year risk assessment in people with 0-1 risk factor is not necessary.

After the LDL-C goal has been achieved, if the TG is still ≥200 mg/dL, non-HDL-C (total-C minus HDL-C) becomes a secondary target of therapy. Non-HDL-C goals are set 30 mg/dL higher than LDL-C goals for each risk category.

Prior to initiating therapy with LIPITOR, secondary causes for hypercholesterolemia (e.g., poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemias, obstructive liver disease, other drug therapy, and alcoholism) should be excluded, and a lipid profile performed to measure total-C, LDL-C, HDL-C, and TG. For patients with TG <400 mg/dL (<4.5 mmol/L), LDL-C can be estimated using the following equation: LDL-C = total-C - (0.20 x [TG] + HDL-C). For TG levels >400 mg/dL (>4.5 mmol/L), this equation is less accurate and LDL-C concentrations should be determined by ultracentrifugation.

LIPITOR has not been studied in conditions where the major lipoprotein abnormality is elevation of chylomicrons *(Fredrickson* Types I and V).

The NCEP classification of cholesterol levels in pediatric patients with a familial history of hypercholesterolemia or premature cardiovascular disease is summarized below:

Category	Total-C (mg/dL)	LDL-C (mg/dL)
Acceptable	<170	<110
Borderline	170-199	110-129
High	≥200	≥130

CONTRAINDICATIONS

Active liver disease or unexplained persistent elevations of serum transaminases.

Hypersensitivity to any component of this medication.

Pregnancy and Lactation

Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). Since HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they may cause fetal harm when administered to pregnant women. Therefore, HMG-CoA reductase inhibitors are contraindicated during pregnancy and in nursing mothers. ATORVASTATIN SHOULD BE ADMINISTERED TO WOMEN OF CHILDBEARING AGE ONLY WHEN SUCH PATIENTS ARE HIGHLY UNLIKELY TO CONCEIVE AND HAVE BEEN INFORMED OF THE POTENTIAL HAZARDS. If the patient becomes pregnant while taking this drug, therapy should be discontinued and the patient apprised of the potential hazard to the fetus.

WARNINGS

Liver Dysfunction

HMG-CoA reductase inhibitors, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. **Persistent elevations (>3 times the upper limit of normal [ULN] occurring on 2 or more occasions) in serum transaminases occurred in 0.7% of patients who received atorvastatin in clinical trials. The incidence of these abnormalities was 0.2%, 0.2%, 0.6%, and 2.3% for 10, 20, 40, and 80 mg, respectively.**

One patient in clinical trials developed jaundice. Increases in liver function tests (LFT) in other patients were not associated with jaundice or other clinical signs or symptoms. Upon dose reduction, drug interruption, or discontinuation, transaminase levels returned to or near pretreatment levels without sequelae. Eighteen of 30 patients with persistent LFT elevations continued treatment with a reduced dose of atorvastatin.

It is recommended that liver function tests be performed prior to and at 12 weeks following both the initiation of therapy and any elevation of dose, and periodically (e.g., semiannually) thereafter. Liver enzyme changes generally occur in the first 3 months of treatment with atorvastatin. Patients who develop increased transaminase levels should be monitored until the abnormalities resolve. Should an increase in ALT or AST of >3 times ULN persist, reduction of dose or withdrawal of atorvastatin is recommended.

Atorvastatin should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease. Active liver disease or unexplained persistent transaminase elevations are contraindications to the use of atorvastatin (see CONTRAINDICATIONS).

Skeletal Muscle

Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with atorvastatin and with other drugs in this class.

Uncomplicated myalgia has been reported in atorvastatin-treated patients (see ADVERSE REACTIONS). Myopathy, defined as muscle aches or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values >10 times ULN, should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. Atorvastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected.

The risk of myopathy during treatment with drugs in this class is increased with concurrent administration of cyclosporine, fibric acid derivatives, erythromycin, clarithromycin, combination of ritonavir plus saquinavir or lopinavir plus ritonavir, niacin, or azole antifungals. Physicians considering combined therapy with atorvastatin and fibric acid derivatives, erythromycin, clarithromycin, a combination of ritonavir plus saquinavir or lopinavir plus ritonavir, immunosuppressive drugs, azole antifungals, or lipid-modifying doses of niacin should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs or symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Lower starting and maintenance doses of atorvastatin should be considered when taken concomitantly with the aforementioned drugs (See DRUG INTERACTIONS). Periodic creatine phosphokinase (CPK) determinations may be considered in such situations, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy.

Atorvastatin therapy should be temporarily withheld or discontinued in any patient with an acute, serious condition suggestive of a myopathy or having a risk factor predisposing to the development of renal failure secondary to rhabdomyolysis (e.g., severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders, and uncontrolled seizures).

PRECAUTIONS

General

Before instituting therapy with atorvastatin, an attempt should be made to control hypercholesterolemia with appropriate diet, exercise, and weight reduction in obese patients, and to treat other underlying medical problems (see INDICATIONS AND USAGE).

Information for Patients

Patients should be advised to report promptly unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever.

Drug Interactions

The risk of myopathy during treatment with HMG-CoA reductase inhibitors is increased with concurrent administration of fibric acid derivatives, lipid-modifying doses of niacin or cytochrome P450 3A4 inhibitors (e.g. cyclosporine, erythromycin, clarithromycin, and azole antifungals) (see WARNINGS, Skeletal Muscle).

Inhibitors of cytochrome P450 3A4: Atorvastatin is metabolized by cytochrome P450 3A4. Concomitant administration of atorvastatin with inhibitors of cytochrome P450 3A4 can lead to increases in plasma concentrations of atorvastatin. The extent of interaction and potentiation of effects depends on the variability of effect on cytochrome P450 3A4.

Clarithromycin: Concomitant administration of atorvastatin 80 mg with clarithromycin (500 mg twice daily) resulted in a 4.4-fold increase in atorvastatin AUC (see WARNINGS, Skeletal Muscle, and DOSAGE AND ADMINISTRATION).

Erythromycin: In healthy individuals, plasma concentrations of atorvastatin increased approximately 40% with co-administration of atorvastatin and erythromycin, a known inhibitor of cytochrome P450 3A4 (see WARNINGS, Skeletal Muscle).

Combination of Protease Inhibitors: Concomitant administration of atorvastatin 40 mg with ritonavir plus saquinavir (400 mg twice daily) resulted in a 3-fold increase in atorvastatin AUC. Concomitant administration of atorvastatin 20 mg with lopinavir plus ritonavir (400 mg+100 mg twice daily) resulted in a 5.9-fold increase in atorvastatin AUC (see WARNINGS, Skeletal Muscle, and DOSAGE AND ADMINISTRATION).

Itraconazole: Concomitant administration of atorvastatin (20 to 40 mg) and itraconazole (200 mg) was associated with a 2.5-3.3-fold increase in atorvastatin AUC.

Diltiazem hydrochloride: Co-administration of atorvastatin (40 mg) with diltiazem (240 mg) was associated with higher plasma concentrations of atorvastatin.

Cimetidine: Atorvastatin plasma concentrations and LDL-C reduction were not altered by co-administration of cimetidine.

Grapefruit juice: Contains one or more components that inhibit CYP 3A4 and can increase plasma concentrations of atorvastatin, especially with excessive grapefruit juice consumption (>1.2 liters per day).

Cyclosporine: Atorvastatin and atorvastatin-metabolites are substrates of the OATP1B1 transporter. Inhibitors of the OATP1B1 (e.g. cyclosporine) can increase the bioavailability of atorvastatin. Concomitant administration of atorvastatin 10 mg and cyclosporine 5.2 mg/kg/day resulted in an 8.7-fold increase in atorvastatin AUC. In cases where co-administration of atorvastatin with cyclosporine is necessary, the dose of atorvastatin should not exceed 10 mg (see WARNINGS, Skeletal Muscle).

Inducers of cytochrome P450 3A4 : Concomitant administration of atorvastatin with inducers of cytochrome P450 3A4 (eg efavirenz, rifampin) can lead to variable reductions in plasma concentrations of atorvastatin. Due to the dual interaction mechanism of rifampin, simultaneous co-administration of atorvastatin with rifampin is recommended, as delayed administration of atorvastatin after administration of rifampin has been associated with a significant reduction in atorvastatin plasma concentrations.

Antacid: When atorvastatin and Maalox® TC suspension were coadministered, plasma concentrations of atorvastatin decreased approximately 35%. However, LDL-C reduction was not altered.

Antipyrine: Because atorvastatin does not affect the pharmacokinetics of antipyrine, interactions with other drugs metabolized via the same cytochrome isozymes are not expected.

Colestipol: Plasma concentrations of atorvastatin decreased approximately 25% when colestipol and atorvastatin were coadministered. However, LDL-C reduction was greater when atorvastatin and colestipol were coadministered than when either drug was given alone.

Digoxin: When multiple doses of atorvastatin and digoxin were coadministered, steady-state plasma digoxin concentrations increased by approximately 20%. Patients taking digoxin should be monitored appropriately.

Oral Contraceptives: Coadministration of atorvastatin and an oral contraceptive increased AUC values for norethindrone and ethinyl estradiol by approximately 30% and 20%. These increases should be considered when selecting an oral contraceptive for a woman taking atorvastatin.

Warfarin: Atorvastatin had no clinically significant effect on prothrombin time when administered to patients receiving chronic warfarin treatment.

Amlodipine: In a drug-drug interaction study in healthy subjects, co-administration of atorvastatin 80 mg and amlodipine 10 mg resulted in an 18% increase in exposure to atorvastatin which was not clinically meaningful.

Endocrine Function

HMG-CoA reductase inhibitors interfere with cholesterol synthesis and theoretically might blunt adrenal and/or gonadal steroid production. Clinical studies have shown that atorvastatin does not reduce basal plasma cortisol concentration or impair adrenal reserve. The effects of HMG-CoA reductase inhibitors on male fertility have not been studied in adequate numbers of patients. The effects, if any, on the pituitary-gonadal axis in premenopausal women are unknown. Caution should be exercised if an HMG-CoA reductase inhibitor is administered concomitantly with drugs that may decrease the levels or activity of endogenous steroid hormones, such as ketoconazole, spironolactone, and cimetidine.

CNS Toxicity

Brain hemorrhage was seen in a female dog treated for 3 months at 120 mg/kg/day. Brain hemorrhage and optic nerve vacuolation were seen in another female dog that was sacrificed in moribund condition after 11 weeks of escalating doses up to 280 mg/kg/day. The 120 mg/kg dose resulted in a systemic exposure approximately 16 times the human plasma area-under-the-curve (AUC, 0-24 hours) based on the maximum human dose of 80 mg/day. A single tonic convulsion was seen in each of 2 male dogs (one treated at 10 mg/kg/day and one at 120 mg/kg/day) in a 2-year study. No CNS lesions have been observed in mice after chronic treatment for up to 2 years at doses up to 400 mg/kg/day or in rats at doses up to 100 mg/kg/day. These doses were 6 to 11 times (mouse) and 8 to 16 times (rat) the human AUC (0-24) based on the maximum recommended human dose of 80 mg/day.

CNS vascular lesions, characterized by perivascular hemorrhages, edema, and mononuclear cell infiltration of perivascular spaces, have been observed in dogs treated with other members of this class. A chemically similar drug in this class produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion at a dose that produced plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 2-year carcinogenicity study in rats at dose levels of 10, 30, and 100 mg/kg/day, 2 rare tumors were found in muscle in high-dose females: in one, there was a rhabdomyosarcoma and, in another, there was a fibrosarcoma. This dose represents a plasma AUC (0-24) value of approximately 16 times the mean human plasma drug exposure after an 80 mg oral dose.

A 2-year carcinogenicity study in mice given 100, 200, or 400 mg/kg/day resulted in a significant increase in liver adenomas in high-dose males and liver carcinomas in high-dose females. These findings occurred at plasma AUC (0-24) values of approximately 6 times the mean human plasma drug exposure after an 80 mg oral dose.

In vitro, atorvastatin was not mutagenic or clastogenic in the following tests with and without metabolic activation: the Ames test with *Salmonella typhimurium* and *Escherichia coli,* the HGPRT forward mutation assay in Chinese hamster lung cells, and the chromosomal aberration assay in Chinese hamster lung cells. Atorvastatin was negative in the *in vivo* mouse micronucleus test.

Studies in rats performed at doses up to 175 mg/kg (15 times the human exposure) produced no changes in fertility. There was aplasia and aspermia in the epididymis of 2 of 10 rats treated with 100 mg/kg/day of atorvastatin for 3 months (16 times the human AUC at the 80 mg dose); testis weights were significantly lower at 30 and 100 mg/kg and epididymal weight was lower at 100 mg/kg. Male rats given 100 mg/kg/day for 11 weeks prior to mating had decreased sperm motility, spermatid head concentration, and increased abnormal sperm. Atorvastatin caused no adverse effects on semen parameters, or reproductive organ histopathology in dogs given doses of 10, 40, or 120 mg/kg for two years.

Pregnancy

Pregnancy Category X

See CONTRAINDICATIONS

Safety in pregnant women has not been established. Atorvastatin crosses the rat placenta and reaches a level in fetal liver equivalent to that of maternal plasma. Atorvastatin was not teratogenic in rats at doses up to 300 mg/kg/day or in rabbits at doses up to 100 mg/kg/day. These doses resulted in multiples of about 30 times (rat) or 20 times (rabbit) the human exposure based on surface area (mg/m^2).

In a study in rats given 20, 100, or 225 mg/kg/day, from gestation day 7 through to lactation day 21 (weaning), there was decreased pup survival at birth, neonate, weaning, and maturity in pups of mothers dosed with 225 mg/kg/day. Body weight was decreased on days 4 and 21 in pups of mothers dosed at 100 mg/kg/day; pup body weight was decreased at birth and at days 4, 21, and 91 at 225 mg/kg/day. Pup development was delayed (rotorod performance at 100 mg/kg/day and acoustic startle at 225 mg/kg/day; pinnae detachment and eye opening at 225 mg/kg/day). These doses correspond to 6 times (100 mg/kg) and 22 times (225 mg/kg) the human AUC at 80 mg/day. Rare reports of congenital anomalies have been received following intrauterine exposure to HMG-CoA reductase inhibitors. There has been one report of severe congenital bony deformity, tracheo-esophageal fistula, and anal atresia (VATER association) in a baby born to a woman who took lovastatin with dextroamphetamine sulfate during the first trimester of pregnancy. LIPITOR should be administered to women of child-bearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the woman becomes pregnant while taking LIPITOR, it should be discontinued and the patient advised again as to the potential hazards to the fetus.

Nursing Mothers

Nursing rat pups had plasma and liver drug levels of 50% and 40%, respectively, of that in their mother's milk. Because of the potential for adverse reactions in nursing infants, women taking LIPITOR should not breast-feed (see CONTRAINDICATIONS).

Pediatric Use

Safety and effectiveness in patients 10-17 years of age with heterozygous familial hypercholesterolemia have been evaluated in a controlled clinical trial of 6 months duration in adolescent boys and postmenarchal girls. Patients treated with LIPITOR had an adverse experience profile generally similar to that of patients treated with placebo, the most common adverse experiences observed in both groups, regardless of causality assessment, were infections. **Doses greater than 20 mg have not been studied in this patient population.** In this limited controlled study, there was no detectable effect on growth or sexual maturation in boys or on menstrual cycle length in girls (see CLINICAL PHARMACOLOGY, Clinical Studies section; ADVERSE REACTIONS, Pediatric Patients (ages 10-17 years); and DOSAGE AND ADMINISTRATION, Heterozygous Familial Hypercholesterolemia in Pediatric Patients (10-17 years of age). Adolescent females should be counseled on appropriate contraceptive methods while on LIPITOR therapy (see CONTRAINDICATIONS and PRECAUTIONS, Pregnancy). **LIPITOR has not been studied in controlled clinical trials involving pre-pubertal patients or patients younger than 10 years of age.**

Clinical efficacy with doses up to 80 mg/day for 1 year have been evaluated in an uncontrolled study of patients with homozygous FH including 8 pediatric patients (see CLINICAL PHARMACOLOGY, Clinical Studies: Homozygous Familial Hypercholesterolemia).

Geriatric Use

The safety and efficacy of atorvastatin (10-80 mg) in the geriatric population (≥65 years of age) was evaluated in the ACCESS study. In this 54-week open-label trial 1,958 patients initiated therapy with atorvastatin 10 mg. Of these, 835 were elderly (≥65 years) and 1,123 were non-elderly. The mean change in LDL-C from baseline after 6 weeks of treatment with atorvastatin 10 mg was –38.2% in the elderly patients versus –34.6% in the non-elderly group.

The rates of discontinuation due to adverse events were similar between the two age groups. There were no differences in clinically relevant laboratory abnormalities between the age groups.

Use in Patients with Recent Stroke or TIA

In a post-hoc analysis of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study where LIPITOR 80 mg vs placebo was administered in 4,731 subjects without CHD who had a stroke or TIA within the preceding 6 months, a higher incidence of hemorrhagic stroke was seen in the LIPITOR 80 mg group compared to

placebo. Subjects with hemorrhagic stroke on study entry appeared to be at increased risk for hemorrhagic stroke.

ADVERSE REACTIONS

LIPITOR is generally well-tolerated. Adverse reactions have usually been mild and transient. In controlled clinical studies of 2502 patients, <2% of patients were discontinued due to adverse experiences attributable to atorvastatin. The most frequent adverse events thought to be related to atorvastatin were constipation, flatulence, dyspepsia, and abdominal pain.

Clinical Adverse Experiences

Adverse experiences reported in ≥2% of patients in placebo-controlled clinical studies of atorvastatin, regardless of causality assessment, are shown in Table 8.

TABLE 8. Adverse Events in Placebo-Controlled Studies (% of Patients)

BODY SYSTEM/ Adverse Event	Placebo N = 270	Atorvastatin 10 mg N = 863	Atorvastatin 20 mg N = 36	Atorvastatin 40 mg N = 79	Atorvastatin 80 mg N = 94
BODY AS A WHOLE					
Infection	10.0	10.3	2.8	10.1	7.4
Headache	7.0	5.4	16.7	2.5	6.4
Accidental Injury	3.7	4.2	0.0	1.3	3.2
Flu Syndrome	1.9	2.2	0.0	2.5	3.2
Abdominal Pain	0.7	2.8	0.0	3.8	2.1
Back Pain	3.0	2.8	0.0	3.8	1.1
Allergic Reaction	2.6	0.9	2.8	1.3	0.0
Asthenia	1.9	2.2	0.0	3.8	0.0
DIGESTIVE SYSTEM					
Constipation	1.8	2.1	0.0	2.5	1.1
Diarrhea	1.5	2.7	0.0	3.8	5.3
Dyspepsia	4.1	2.3	2.8	1.3	2.1
Flatulence	3.3	2.1	2.8	1.3	1.1
RESPIRATORY SYSTEM					
Sinusitis	2.6	2.8	0.0	2.5	6.4
Pharyngitis	1.5	2.5	0.0	1.3	2.1
SKIN AND APPENDAGES					
Rash	0.7	3.9	2.8	3.8	1.1
MUSCULOSKELETAL SYSTEM					
Arthralgia	1.5	2.0	0.0	5.1	0.0
Myalgia	1.1	3.2	5.6	1.3	0.0

Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT)
In ASCOT (see CLINICAL PHARMACOLOGY, *Clinical Studies*) involving 10,305 participants treated with LIPITOR 10 mg daily (n=5,168) or placebo (n=5,137), the safety and tolerability profile of the group treated with LIPITOR was comparable to that of the group treated with placebo during a median of 3.3 years of follow-up.

Collaborative Atorvastatin Diabetes Study (CARDS)
In CARDS (see CLINICAL PHARMACOLOGY, *Clinical Studies*) involving 2838 subjects with type 2 diabetes treated with LIPITOR 10 mg daily (n=1428) or placebo (n=1410), there was no difference in the overall frequency of adverse events or serious adverse events between the treatment groups during a median follow-up of 3.9 years. No cases of rhabdomyolysis were reported.

Treating to New Targets Study (TNT)
In TNT (see CLINICAL PHARMACOLOGY, *Clinical Studies*) involving 10,001 subjects with clinically evident CHD treated with LIPITOR 10 mg daily (n=5006) or LIPITOR 80 mg daily (n=4995), there were more serious adverse events and discontinuations due to adverse events in the high-dose atorvastatin group (92, 1.8%; 497, 9.9%, respectively) as compared to the low-dose group (69, 1.4%; 404, 8.1%, respectively) during a median follow-up of 4.9 years. Persistent transaminase elevations (≥3 x ULN twice within 4-10 days) occurred in 62 (1.3%) individuals with atorvastatin 80 mg and in nine (0.2%) individuals with atorvastatin 10 mg. Elevations of CK (≥ 10 x ULN) were low overall, but were higher in the high-dose atorvastatin treatment group (13, 0.3%) compared to the low-dose atorvastatin group (6, 0.1%).

Incremental Decrease in Endpoints Through Aggressive Lipid Lowering Study (IDEAL)
In IDEAL (see CLINICAL PHARMACOLOGY, *Clinical Studies*) involving 8,888 subjects treated with LIPITOR 80 mg/day (n=4439) or simvastatin 20-40 mg daily (n=4449), there was no difference in the overall frequency of adverse events or serious adverse events between the treatment groups during a median follow-up of 4.8 years.

The following adverse events were reported, regardless of causality assessment in patients treated with atorvastatin in clinical trials. The events in italics occurred in ≥2% of patients and the events in plain type occurred in <2% of patients.

Body as a Whole: *Chest pain*, face edema, fever, neck rigidity, malaise, photosensitivity reaction, generalized edema.

Digestive System: *Nausea,* gastroenteritis, liver function tests abnormal, colitis, vomiting, gastritis, dry mouth, rectal hemorrhage, esophagitis, eructation, glossitis, mouth ulceration, anorexia, increased appetite, stomatitis, biliary pain, cheilitis, duodenal ulcer, dysphagia, enteritis, melena, gum hemorrhage, stomach ulcer, tenesmus, ulcerative stomatitis, hepatitis, pancreatitis, cholestatic jaundice.

Respiratory System: *Bronchitis, rhinitis,* pneumonia, dyspnea, asthma, epistaxis.

Nervous System: *Insomnia, dizziness,* paresthesia, somnolence, amnesia, abnormal dreams, libido decreased, emotional lability, incoordination, peripheral neuropathy, torticollis, facial paralysis, hyperkinesia, depression, hypesthesia, hypertonia.

Musculoskeletal System: *Arthritis,* leg cramps, bursitis, tenosynovitis, myasthenia, tendinous contracture, myositis.

Skin and Appendages: Pruritus, contact dermatitis, alopecia, dry skin, sweating, acne, urticaria, eczema, seborrhea, skin ulcer.

Urogenital System: *Urinary tract infection, hematuria, albuminuria,* urinary frequency, cystitis, impotence, dysuria, kidney calculus, nocturia, epididymitis, fibrocystic breast,

vaginal hemorrhage, breast enlargement, metrorrhagia, nephritis, urinary incontinence, urinary retention, urinary urgency, abnormal ejaculation, uterine hemorrhage.

Special Senses: Amblyopia, tinnitus, dry eyes, refraction disorder, eye hemorrhage, deafness, glaucoma, parosmia, taste loss, taste perversion.

Cardiovascular System: Palpitation, vasodilatation, syncope, migraine, postural hypotension, phlebitis, arrhythmia, angina pectoris, hypertension.

Metabolic and Nutritional Disorders: *Peripheral edema,* hyperglycemia, creatine phosphokinase increased, gout, weight gain, hypoglycemia.

Hemic and Lymphatic System: Ecchymosis, anemia, lymphadenopathy, thrombocytopenia, petechia.

Postintroduction Reports

Adverse events associated with LIPITOR therapy reported since market introduction, that are not listed above, regardless of causality assessment, include the following: anaphylaxis, angioneurotic edema, bullous rashes (including erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis), rhabdomyolysis, fatigue, and tendon rupture.

Pediatric Patients (ages 10-17 years)
In a 26-week controlled study in boys and postmenarchal girls (n=140), the safety and tolerability profile of LIPITOR 10 to 20 mg daily was generally similar to that of placebo (see CLINICAL PHARMACOLOGY, Clinical Studies section and PRECAUTIONS, Pediatric Use).

OVERDOSAGE

There is no specific treatment for atorvastatin overdosage. In the event of an overdose, the patient should be treated symptomatically, and supportive measures instituted as required. Due to extensive drug binding to plasma proteins, hemodialysis is not expected to significantly enhance atorvastatin clearance.

DOSAGE AND ADMINISTRATION

The patient should be placed on a standard cholesterol-lowering diet before receiving LIPITOR and should continue on this diet during treatment with LIPITOR.

Hypercholesterolemia (Heterozygous Familial and Nonfamilial) and Mixed Dyslipidemia *(Fredrickson* Types IIa and IIb)

The recommended starting dose of LIPITOR is 10 or 20 mg once daily. Patients who require a large reduction in LDL-C (more than 45%) may be started at 40 mg once daily.

The dosage range of LIPITOR is 10 to 80 mg once daily. LIPITOR can be administered as a single dose at any time of the day, with or without food. The starting dose and maintenance doses of LIPITOR should be individualized according to patient characteristics such as goal of therapy and response (see *NCEP Guidelines,* summarized in Table 7). After initiation and/or upon titration of LIPITOR, lipid levels should be analyzed within 2 to 4 weeks and dosage adjusted accordingly.

Since the goal of treatment is to lower LDL-C, the NCEP recommends that LDL-C levels be used to initiate and assess treatment response. Only if LDL-C levels are not available, should total-C be used to monitor therapy.

Heterozygous Familial Hypercholesterolemia in Pediatric Patients (10-17 years of age)

The recommended starting dose of LIPITOR is 10 mg/day; the maximum recommended dose is 20 mg/day (doses greater than 20 mg have not been studied in this patient population). Doses should be individualized according to the recommended goal of therapy (see NCEP Pediatric Panel Guidelines[i], CLINICAL PHARMACOLOGY, and INDICATIONS AND USAGE). Adjustments should be made at intervals of 4 weeks or more.

Homozygous Familial Hypercholesterolemia

The dosage of LIPITOR in patients with homozygous FH is 10 to 80 mg daily. LIPITOR should be used as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) in these patients or if such treatments are unavailable.

Concomitant Lipid Lowering Therapy

LIPITOR may be used in combination with a bile acid binding resin for additive effect. The combination of HMG-CoA reductase inhibitors and fibrates should generally be avoided (see WARNINGS, Skeletal Muscle, and PRECAUTIONS, Drug Interactions for other drug-drug interactions).

Dosage in Patients With Renal Insufficiency

Renal disease does not affect the plasma concentrations nor LDL-C reduction of atorvastatin; thus, dosage adjustment in patients with renal dysfunction is not necessary (see CLINICAL PHARMACOLOGY, Pharmacokinetics).

Dosage in Patients Taking Cyclosporine, Clarithromycin or A Combination of Ritonavir plus Saquinavir or Lopinavir plus Ritonavir

In patients taking cyclosporine, therapy should be limited to LIPITOR 10 mg once daily. In patients taking clarithromycin or in patients with HIV taking a combination of ritonavir plus saquinavir or lopinavir plus ritonavir, for doses of atorvastatin exceeding 20 mg appropriate clinical assessment is recommended to ensure that the lowest dose

necessary of atorvastatin is employed (see WARNINGS, Skeletal Muscle, and PRECAUTIONS, Drug Interactions).

HOW SUPPLIED

LIPITOR® (atorvastatin calcium) is supplied as white, elliptical, film-coated tablets of atorvastatin calcium containing 10, 20, 40 and 80 mg atorvastatin.

10 mg tablets: coded "PD 155" on one side and "10" on the other.
NDC 0071-0155-23 bottles of 90
NDC 0071-0155-34 bottles of 5000
NDC 0071-0155-40 10 x 10 unit dose blisters

20 mg tablets: coded "PD 156" on one side and "20" on the other.
NDC 0071-0156-23 bottles of 90
NDC 0071-0156-40 10 x 10 unit dose blisters
NDC 0071-0156-94 bottles of 5000

40 mg tablets: coded "PD 157" on one side and "40" on the other.
NDC 0071-0157-23 bottles of 90
NDC 0071-0157-73 bottles of 500
NDC 0071-0157-88 bottles of 2500
NDC 0071-0157-40 10 x 10 unit dose blisters

80 mg tablets: coded "PD 158" on one side and "80" on the other.
NDC 0071-0158-23 bottles of 90
NDC 0071-0158-73 bottles of 500
NDC 0071-0158-88 bottles of 2500
NDC 0071-0158-92 8 x 8 unit dose blisters

Storage
Store at controlled room temperature 20 - 25°C (68 - 77°F) [see USP].

Rx Only

Manufactured by:
Pfizer Ireland Pharmaceuticals
Dublin, Ireland

Distributed by:

Pfizer
Parke-Davis
Division of Pfizer Inc, NY, NY 10017

EXHIBIT F

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-540

Pfizer Inc.
Attention: Mr. Robert Clark
235 East 42nd Street
New York, NY 10017

Dear Mr. Clark:

Please refer to your new drug application (NDA) dated March 31, 2003, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Caduet (amlodipine besylate/atorvastatin calcium) 5/10, 10/10, 5/20, 10/20, 5/40, 10/40, 5/80 and 10/80 mg Tablets.

We acknowledge receipt of your submissions dated June 30, July 8, 31, August 7, 8 (two), 11, 18, September 24, 26 (two), October 9, 10, 20, 31 (two), November 5, 11 (two), 12 (two), 19, December 12 (two), 19 (two), 2003, January 16, 20 (two), 21, 26, 28 (two), and 30, 2004.

This new drug application provides for the use of Caduet (amlodipine besylate/atorvastatin calcium) in patients for whom treatment with both amlodipine and atorvastatin is appropriate as indicated in the agreed-upon labeling.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling text for the package insert. Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission **"FPL for approved NDA 21-540."** Approval of this submission by FDA is not required before the labeling is used.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division/ the Division of Cardio-Renal Drug Products and two copies of both the promotional materials and the package insert(s) directly to:

Division of Drug Marketing, Advertising,
and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

(
b)(4)----------
---------- ---------- ----------

-

The proposed dissolution method and specifications are as follows: USP Type II apparatus at a paddle speed of 75 rpm in 900 mL of phosphate buffer pH 6.8 with a Q of (b) in 15 minutes for both amlodipine and atorvastatin.

An expiration date of 18 months is granted for CADUET tablets 5/10, 5/20, 5/40, 5/80, 10/10, 10/20, 10/40 and 10/80 mg, packaged in foil/foil blisters and HDPE bottles of 30 tablets. Any extension of the expiration date beyond 18 months should be based on real-time stability data generated according to the amended post-approval stability protocol dated January 28, 2004.

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have fulfilled the pediatric study requirement for this application.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please call Ms. Denise M. Hinton, Regulatory Health Project Manager, at (301) 594-5333.

Sincerely,

{See appended electronic signature page}

Douglas C. Throckmorton, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure: Draft label

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Norman Stockbridge
1/30/04 02:44:18 PM
For Douglas Throckmorton

EXHIBIT G

CADUET®
(amlodipine besylate/atorvastatin calcium) Tablets

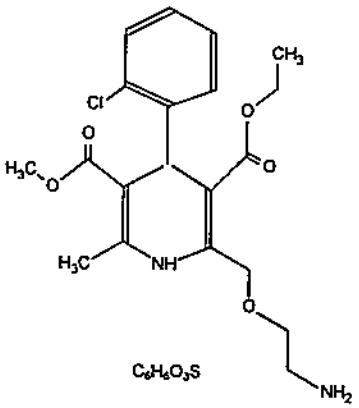
DESCRIPTION

CADUET® (amlodipine besylate and atorvastatin calcium) tablets combine the long-acting calcium channel blocker amlodipine besylate with the synthetic lipid-lowering agent atorvastatin calcium.

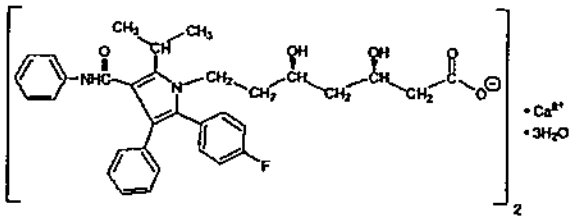
The amlodipine besylate component of CADUET is chemically described as 3-Ethyl-5-methyl (±)-2-[(2-aminoethoxy)methyl]-4-(o-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate, monobenzenesulphonate. Its empirical formula is $C_{20}H_{25}ClN_2O_5 \bullet C_6H_6O_3S$.

The atorvastatin calcium component of CADUET is chemically described as [R-(R*, R*)]-2-(4-fluorophenyl)-ß, δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid, calcium salt (2:1) trihydrate. Its empirical formula is $(C_{33}H_{34}FN_2O_5)_2Ca \bullet 3H_2O$.

The structural formulae for amlodipine besylate and atorvastatin calcium are shown below.



Amlodipine besylate



Atorvastatin calcium

CADUET contains amlodipine besylate, a white to off-white crystalline powder, and atorvastatin calcium, also a white to off-white crystalline powder. Amlodipine besylate has a molecular weight of 567.1 and atorvastatin calcium has a molecular weight of 1209.42. Amlodipine besylate is slightly soluble in water and sparingly soluble in ethanol. Atorvastatin calcium is insoluble in aqueous solutions of pH 4 and below. Atorvastatin calcium is very slightly soluble in distilled water, pH 7.4 phosphate buffer, and acetonitrile; slightly soluble in ethanol, and freely soluble in methanol.

CADUET tablets are formulated for oral administration in the following strength combinations:

Table 1. CADUET Tablet Strengths

	2.5 mg/ 10mg	2.5 mg/ 20mg	2.5 mg/ 40mg	5 mg/10 mg	5 mg/20 mg	5 mg/40 mg	5 mg/80 mg	10 mg/ 10 mg	10 mg/ 20 mg	10 mg/ 40 mg	10 mg/ 80 mg
amlodipine equivalent (mg)	2.5	2.5	2.5	5	5	5	5	10	10	10	10
atorvastatin equivalent (mg)	10	20	40	10	20	40	80	10	20	40	80

Each tablet also contains calcium carbonate, croscarmellose sodium, microcrystalline cellulose, pregelatinized starch, polysorbate 80, hydroxypropyl cellulose, purified water, colloidal silicon dioxide (anhydrous), magnesium stearate, Opadry® II White 85F28751 (polyvinyl alcohol, titanium dioxide, PEG 3000 and talc) or Opadry® II Blue 85F10919 (polyvinyl alcohol, titanium dioxide, PEG 3000, talc and FD&C blue #2). Combinations of atorvastatin with 2.5 mg and 5 mg amlodipine are film coated white, and combinations of atorvastatin with 10 mg amlodipine are film coated blue.

CLINICAL PHARMACOLOGY

Mechanism of Action

CADUET

CADUET is a combination of two drugs, a dihydropyridine calcium antagonist (calcium ion antagonist or slow-channel blocker) amlodipine (antihypertensive/antianginal agent) and an HMG-CoA reductase inhibitor atorvastatin (cholesterol lowering agent). The amlodipine component of CADUET inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. The atorvastatin component of CADUET is a selective, competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methylglutaryl-coenzyme A to mevalonate, a precursor of sterols, including cholesterol.

The Amlodipine Component of CADUET

Experimental data suggest that amlodipine binds to both dihydropyridine and nondihydropyridine binding sites. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels. Amlodipine inhibits calcium ion influx across cell membranes selectively, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells. Negative inotropic effects can be detected *in vitro* but such effects have not been seen in intact animals at therapeutic doses. Serum calcium concentration is not affected by amlodipine. Within the physiologic pH range, amlodipine is an ionized

compound (pKa=8.6), and its kinetic interaction with the calcium channel receptor is characterized by a gradual rate of association and dissociation with the receptor binding site, resulting in a gradual onset of effect.

Amlodipine is a peripheral arterial vasodilator that acts directly on vascular smooth muscle to cause a reduction in peripheral vascular resistance and reduction in blood pressure.

The precise mechanisms by which amlodipine relieves angina have not been fully delineated, but are thought to include the following:

Exertional Angina: In patients with exertional angina, amlodipine reduces the total peripheral resistance (afterload) against which the heart works and reduces the rate pressure product, and thus myocardial oxygen demand, at any given level of exercise.

Vasospastic Angina: Amlodipine has been demonstrated to block constriction and restore blood flow in coronary arteries and arterioles in response to calcium, potassium epinephrine, serotonin, and thromboxane A_2 analog in experimental animal models and in human coronary vessels *in vitro*. This inhibition of coronary spasm is responsible for the effectiveness of amlodipine in vasospastic (Prinzmetal's or variant) angina.

The Atorvastatin Component of CADUET

Cholesterol and triglycerides circulate in the bloodstream as part of lipoprotein complexes. With ultracentrifugation, these complexes separate into HDL (high-density lipoprotein), IDL (intermediate-density lipoprotein), LDL (low-density lipoprotein), and VLDL (very-low-density lipoprotein) fractions. Triglycerides (TG) and cholesterol in the liver are incorporated into VLDL and released into the plasma for delivery to peripheral tissues. LDL is formed from VLDL and is catabolized primarily through the high-affinity LDL receptor.

Clinical and pathologic studies show that elevated plasma levels of total cholesterol (total-C), LDL-cholesterol (LDL-C), and apolipoprotein B (apo B) promote human atherosclerosis and are risk factors for developing cardiovascular disease, while increased levels of HDL-C are associated with a decreased cardiovascular risk.

Epidemiologic investigations have established that cardiovascular morbidity and mortality vary directly with the level of total-C and LDL-C, and inversely with the level of HDL-C.

In animal models, atorvastatin lowers plasma cholesterol and lipoprotein levels by inhibiting HMG-CoA reductase and cholesterol synthesis in the liver and by increasing the number of hepatic LDL receptors on the cell-surface to enhance uptake and catabolism of LDL; atorvastatin also reduces LDL production and the number of LDL particles.

Atorvastatin reduces total-C, LDL-C, and apo B in patients with homozygous and heterozygous familial hypercholesterolemia (FH), nonfamilial forms of hypercholesterolemia, and mixed dyslipidemia. Atorvastatin also reduces VLDL-C and TG

and produces variable increases in HDL-C and apolipoprotein A-1. Atorvastatin reduces total-C, LDL-C, VLDL-C, apo B, TG, and non-HDL-C, and increases HDL-C in patients with isolated hypertriglyceridemia. Atorvastatin reduces intermediate density lipoprotein cholesterol (IDL-C) in patients with dysbetalipoproteinemia.

Like LDL, cholesterol-enriched triglyceride-rich lipoproteins, including VLDL, intermediate density lipoprotein (IDL), and remnants, can also promote atherosclerosis. Elevated plasma triglycerides are frequently found in a triad with low HDL-C levels and small LDL particles, as well as in association with non-lipid metabolic risk factors for coronary heart disease. As such, total plasma TG has not consistently been shown to be an independent risk factor for CHD. Furthermore, the independent effect of raising HDL or lowering TG on the risk of coronary and cardiovascular morbidity and mortality has not been determined.

Pharmacokinetics and Metabolism

Absorption

Studies with amlodipine: After oral administration of therapeutic doses of amlodipine alone, absorption produces peak plasma concentrations between 6 and 12 hours. Absolute bioavailability has been estimated to be between 64% and 90%. The bioavailability of amlodipine when administered alone is not altered by the presence of food.

Studies with atorvastatin: After oral administration alone, atorvastatin is rapidly absorbed; maximum plasma concentrations occur within 1 to 2 hours. Extent of absorption increases in proportion to atorvastatin dose. The absolute bioavailability of atorvastatin (parent drug) is approximately 14% and the systemic availability of HMG-CoA reductase inhibitory activity is approximately 30%. The low systemic availability is attributed to presystemic clearance in gastrointestinal mucosa and/or hepatic first-pass metabolism. Although food decreases the rate and extent of drug absorption by approximately 25% and 9%, respectively, as assessed by Cmax and AUC, LDL-C reduction is similar whether atorvastatin is given with or without food. Plasma atorvastatin concentrations are lower (approximately 30% for Cmax and AUC) following evening drug administration compared with morning. However, LDL-C reduction is the same regardless of the time of day of drug administration (see **DOSAGE AND ADMINISTRATION**).

Studies with CADUET: Following oral administration of CADUET peak plasma concentrations of amlodipine and atorvastatin are seen at 6 to 12 hours and 1 to 2 hours post dosing, respectively. The rate and extent of absorption (bioavailability) of amlodipine and atorvastatin from CADUET are not significantly different from the bioavailability of amlodipine and atorvastatin administered separately (see above).

The bioavailability of amlodipine from CADUET was not affected by food. Although food decreases the rate and extent of absorption of atorvastatin from CADUET by approximately 32% and 11%, respectively, as it does with atorvastatin when given alone. LDL-C reduction is similar whether atorvastatin is given with or without food.

Distribution

Studies with amlodipine: Ex vivo studies have shown that approximately 93% of the circulating amlodipine drug is bound to plasma proteins in hypertensive patients. Steady-state plasma levels of amlodipine are reached after 7 to 8 days of consecutive daily dosing.

Studies with atorvastatin: Mean volume of distribution of atorvastatin is approximately 381 liters. Atorvastatin is ≥98% bound to plasma proteins. A blood/plasma ratio of approximately 0.25 indicates poor drug penetration into red blood cells. Based on observations in rats, atorvastatin calcium is likely to be secreted in human milk (see **CONTRAINDICATIONS, Pregnancy and Lactation,** and **PRECAUTIONS, Nursing Mothers**).

Metabolism

Studies with amlodipine: Amlodipine is extensively (about 90%) converted to inactive metabolites via hepatic metabolism.

Studies with atorvastatin: Atorvastatin is extensively metabolized to ortho- and parahydroxylated derivatives and various beta-oxidation products. *In vitro* inhibition of HMG-CoA reductase by ortho- and parahydroxylated metabolites is equivalent to that of atorvastatin. Approximately 70% of circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites. *In vitro* studies suggest the importance of atorvastatin metabolism by cytochrome P450 3A4, consistent with increased plasma concentrations of atorvastatin in humans following coadministration with erythromycin, a known inhibitor of this isozyme (see **PRECAUTIONS, Drug Interactions**). In animals, the ortho-hydroxy metabolite undergoes further glucuronidation.

Excretion

Studies with amlodipine: Elimination from the plasma is biphasic with a terminal elimination half-life of about 30-50 hours. Ten percent of the parent amlodipine compound and 60% of the metabolites of amlodipine are excreted in the urine.

Studies with atorvastatin: Atorvastatin and its metabolites are eliminated primarily in bile following hepatic and/or extra-hepatic metabolism; however, the drug does not appear to undergo enterohepatic recirculation. Mean plasma elimination half-life of atorvastatin in humans is approximately 14 hours, but the half-life of inhibitory activity for HMG-CoA reductase is 20 to 30 hours due to the contribution of active metabolites. Less than 2% of a dose of atorvastatin is recovered in urine following oral administration.

Special Populations

Geriatric

Studies with amlodipine: Elderly patients have decreased clearance of amlodipine with a resulting increase in AUC of approximately 40-60%, and a lower initial dose of amlodipine may be required.

Studies with atorvastatin: Plasma concentrations of atorvastatin are higher (approximately 40% for Cmax and 30% for AUC) in healthy elderly subjects (age ≥65 years) than in young adults. Clinical data suggest a greater degree of LDL-lowering at any dose of atorvastatin in the elderly population compared to younger adults (see **PRECAUTIONS** section, **Geriatric Use**).

Pediatric

Studies with amlodipine: Sixty-two hypertensive patients aged 6 to 17 years received doses of amlodipine between 1.25 mg and 20 mg. Weight-adjusted clearance and volume of distribution were similar to values in adults.

Studies with atorvastatin: Pharmacokinetic data in the pediatric population are not available.

Gender

Studies with atorvastatin: Plasma concentrations of atorvastatin in women differ from those in men (approximately 20% higher for Cmax and 10% lower for AUC); however, there is no clinically significant difference in LDL-C reduction with atorvastatin between men and women.

Renal Insufficiency

Studies with amlodipine: The pharmacokinetics of amlodipine are not significantly influenced by renal impairment. Patients with renal failure may therefore receive the usual initial amlodipine dose.

Studies with atorvastatin: Renal disease has no influence on the plasma concentrations or LDL-C reduction of atorvastatin; thus, dose adjustment of atorvastatin in patients with renal dysfunction is not necessary (see **DOSAGE AND ADMINISTRATION**).

Hemodialysis

While studies have not been conducted in patients with end-stage renal disease, hemodialysis is not expected to significantly enhance clearance of atorvastatin and/or amlodipine since both drugs are extensively bound to plasma proteins.

Hepatic Insufficiency

Studies with amlodipine: Elderly patients and patients with hepatic insufficiency have decreased clearance of amlodipine with a resulting increase in AUC of approximately 40-60%, and a lower initial dose may be required.

Studies with atorvastatin: In patients with chronic alcoholic liver disease, plasma concentrations of atorvastatin are markedly increased. Cmax and AUC are each 4-fold greater in patients with Childs-Pugh A disease. Cmax and AUC of atorvastatin are approximately 16-fold and 11-fold increased, respectively, in patients with Childs-Pugh B disease (see **CONTRAINDICATIONS**).

Heart Failure

Studies with amlodipine: In patients with moderate to severe heart failure, the increase in AUC for amlodipine was similar to that seen in the elderly and in patients with hepatic insufficiency.

Pharmacodynamics

Hemodynamic Effects of Amlodipine: Following administration of therapeutic doses to patients with hypertension, amlodipine produces vasodilation resulting in a reduction of supine and standing blood pressures. These decreases in blood pressure are not accompanied by a significant change in heart rate or plasma catecholamine levels with chronic dosing. Although the acute intravenous administration of amlodipine decreases arterial blood pressure and increases heart rate in hemodynamic studies of patients with chronic stable angina, chronic administration of oral amlodipine in clinical trials did not lead to clinically significant changes in heart rate or blood pressures in normotensive patients with angina.

With chronic once daily oral administration of amlodipine, antihypertensive effectiveness is maintained for at least 24 hours. Plasma concentrations correlate with effect in both young and elderly patients. The magnitude of reduction in blood pressure with amlodipine is also correlated with the height of pretreatment elevation; thus, individuals with moderate hypertension (diastolic pressure 105-114 mmHg) had about a 50% greater response than patients with mild hypertension (diastolic pressure 90-104 mmHg). Normotensive subjects experienced no clinically significant change in blood pressures (+1/–2 mmHg).

In hypertensive patients with normal renal function, therapeutic doses of amlodipine resulted in a decrease in renal vascular resistance and an increase in glomerular filtration rate and effective renal plasma flow without change in filtration fraction or proteinuria.

As with other calcium channel blockers, hemodynamic measurements of cardiac function at rest and during exercise (or pacing) in patients with normal ventricular function treated with amlodipine have generally demonstrated a small increase in cardiac index without

significant influence on dP/dt or on left ventricular end diastolic pressure or volume. In hemodynamic studies, amlodipine has not been associated with a negative inotropic effect when administered in the therapeutic dose range to intact animals and man, even when co-administered with beta-blockers to man. Similar findings, however, have been observed in normals or well-compensated patients with heart failure with agents possessing significant negative inotropic effects.

Electrophysiologic Effects of Amlodipine: Amlodipine does not change sinoatrial nodal function or atrioventricular conduction in intact animals or man. In patients with chronic stable angina, intravenous administration of 10 mg did not significantly alter A-H and H-V conduction and sinus node recovery time after pacing. Similar results were obtained in patients receiving amlodipine and concomitant beta blockers. In clinical studies in which amlodipine was administered in combination with beta-blockers to patients with either hypertension or angina, no adverse effects on electrocardiographic parameters were observed. In clinical trials with angina patients alone, amlodipine therapy did not alter electrocardiographic intervals or produce higher degrees of AV blocks.

LDL-C Reduction with Atorvastatin: Atorvastatin as well as some of its metabolites are pharmacologically active in humans. The liver is the primary site of action and the principal site of cholesterol synthesis and LDL clearance. Drug dosage rather than systemic drug concentration correlates better with LDL-C reduction. Individualization of drug dosage should be based on therapeutic response (see **DOSAGE AND ADMINISTRATION**).

Clinical Studies

Clinical Studies with Amlodipine

Amlodipine Effects in Hypertension

Adult Patients: The antihypertensive efficacy of amlodipine has been demonstrated in a total of 15 double-blind, placebo-controlled, randomized studies involving 800 patients on amlodipine and 538 on placebo. Once daily administration produced statistically significant placebo-corrected reductions in supine and standing blood pressures at 24 hours postdose, averaging about 12/6 mmHg in the standing position and 13/7 mmHg in the supine position in patients with mild to moderate hypertension. Maintenance of the blood pressure effect over the 24-hour dosing interval was observed, with little difference in peak and trough effect. Tolerance was not demonstrated in patients studied for up to 1 year. The 3 parallel, fixed doses, dose response studies showed that the reduction in supine and standing blood pressures was dose-related within the recommended dosing range. Effects on diastolic pressure were similar in young and older patients. The effect on systolic pressure was greater in older patients, perhaps because of greater baseline systolic pressure. Effects were similar in black patients and in white patients.

Pediatric Patients: Two-hundred sixty-eight hypertensive patients aged 6 to 17 years were randomized first to amlodipine 2.5 or 5 mg once daily for 4 weeks and then randomized again to the same dose or to placebo for another 4 weeks. Patients receiving 5 mg

amlodipine at the end of 8 weeks had lower blood pressure than those secondarily randomized to placebo. The magnitude of the treatment effect is difficult to interpret, but it is probably less than 5 mmHg systolic on the 5 mg dose. Adverse events were similar to those seen in adults.

Amlodipine Effects in Chronic Stable Angina: The effectiveness of 5-10 mg/day of amlodipine in exercise-induced angina has been evaluated in 8 placebo-controlled, double-blind clinical trials of up to 6 weeks duration involving 1038 patients (684 amlodipine, 354 placebo) with chronic stable angina. In 5 of the 8 studies, significant increases in exercise time (bicycle or treadmill) were seen with the 10 mg dose. Increases in symptom-limited exercise time averaged 12.8% (63 sec) for amlodipine 10 mg, and averaged 7.9% (38 sec) for amlodipine 5 mg. Amlodipine 10 mg also increased time to 1 mm ST segment deviation in several studies and decreased angina attack rate. The sustained efficacy of amlodipine in angina patients has been demonstrated over long-term dosing. In patients with angina, there were no clinically significant reductions in blood pressures (4/1 mmHg) or changes in heart rate (+0.3 bpm).

Amlodipine Effects in Vasospastic Angina: In a double-blind, placebo-controlled clinical trial of 4 weeks duration in 50 patients, amlodipine therapy decreased attacks by approximately 4/week compared with a placebo decrease of approximately 1/week ($p<0.01$). Two of 23 amlodipine and 7 of 27 placebo patients discontinued from the study due to lack of clinical improvement.

Amlodipine Effects in Documented Coronary Artery Disease: In PREVENT, 825 patients with angiographically documented coronary artery disease were randomized to amlodipine (5-10 mg once daily) or placebo and followed for 3 years. Although the study did not show significance on the primary objective of change in coronary luminal diameter as assessed by quantitative coronary angiography, the data suggested a favorable outcome with respect to fewer hospitalizations for angina and revascularization procedures in patients with CAD.

CAMELOT enrolled 1318 patients with CAD recently documented by angiography, without left main coronary disease and without heart failure or an ejection fraction <40%. Patients (76% males, 89% Caucasian, 93% enrolled at US sites, 89% with a history of angina, 52% without PCI, 4% with PCI and no stent, and 44% with a stent) were randomized to double-blind treatment with either amlodipine (5 – 10 mg once daily) or placebo in addition to standard care that included aspirin (89%), statins (83%), beta-blockers (74%), nitroglycerin (50%), anti-coagulants (40%), and diuretics (32%), but excluded other calcium channel blockers. The mean duration of follow-up was 19 months. The primary endpoint was the time to first occurrence of one of the following events: hospitalization for angina pectoris, coronary revascularization, myocardial infarction, cardiovascular death, resuscitated cardiac arrest, hospitalization for heart failure, stroke/TIA, or peripheral vascular disease. A total of 110 (16.6%) and 151 (23.1%) first events occurred in the amlodipine and placebo groups respectively for a hazard ratio of 0.691 (95% CI: 0.540-0.884, p= 0.003). The primary endpoint is summarized in Figure 1 below. The outcome of this study was largely derived from the prevention of hospitalizations for angina and the prevention of revascularization procedures (see Table 2). Effects in various subgroups are shown in Figure 2.

In an angiographic substudy (n=274) conducted within CAMELOT, there was no significant difference between amlodipine and placebo on the change of atheroma volume in the coronary artery as assessed by intravascular ultrasound.

Figure 1: Kaplan-Meier analysis of composite clinical outcomes for amlodipine versus placebo

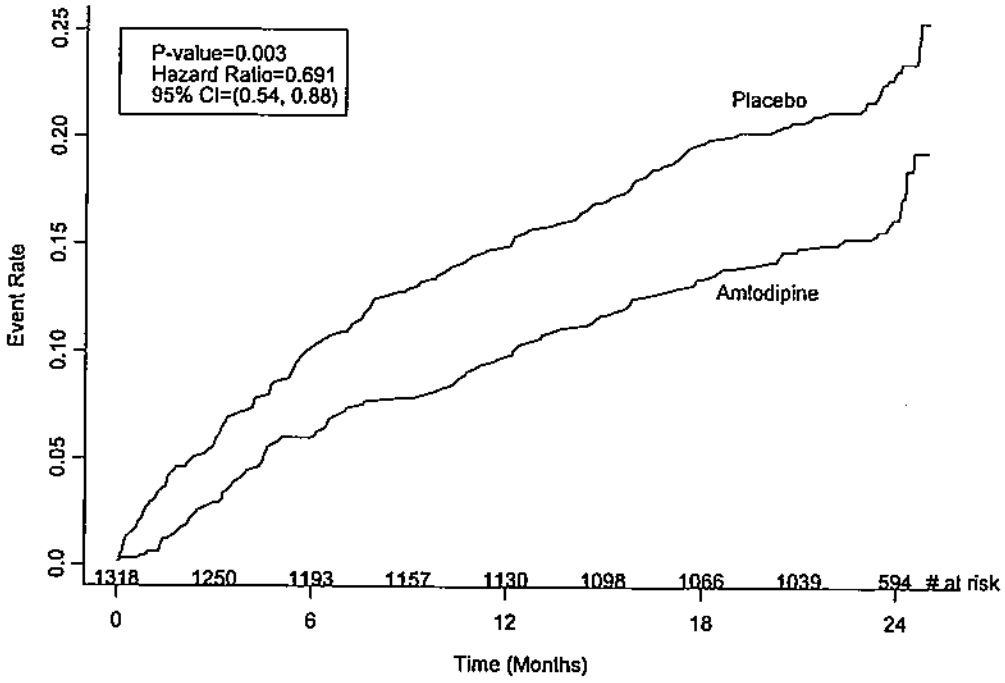
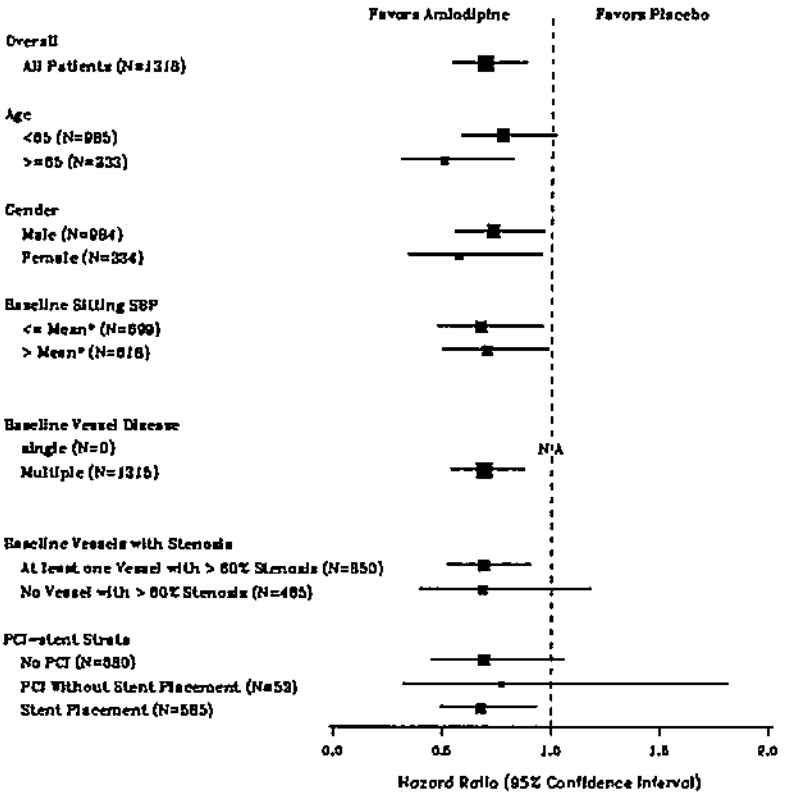


Figure 2 – Effects on primary endpoint of amlodipine versus placebo across sub-groups



*The mean sitting baseline SBP is 129 mmHg

Table 2 below summarizes the significant clinical outcomes from the composites of the primary endpoint. The other components of the primary endpoint including cardiovascular death, resuscitated cardiac arrest, myocardial infarction, hospitalization for heart failure, stroke/TIA, or peripheral vascular disease did not demonstrate a significant difference between amlodipine and placebo.

Table 2. Incidence of Significant Clinical Outcomes for CAMELOT

Clinical Outcomes N (%)	Amlodipine (N=663)	Placebo (N=655)	Risk Reduction (p-value)
Composite CV Endpoint	**110 (16.6)**	**151 (23.1)**	**31% (0.003)**
Hospitalization for Angina*	51 (7.7)	84 (12.8)	42% (0.002)
Coronary Revascularization*	78 (11.8)	103 (15.7)	27% (0.033)

*Total patients with these events

Amlodipine Effects in Patients with Congestive Heart Failure: Amlodipine has been compared to placebo in four 8-12 week studies of patients with NYHA class II/III heart failure, involving a total of 697 patients. In these studies, there was no evidence of worsened heart failure based on measures of exercise tolerance, NYHA classification, symptoms, or LVEF. In a long-term (follow-up at least 6 months, mean 13.8 months) placebo-controlled mortality/morbidity study of amlodipine 5-10 mg in 1153 patients with NYHA classes III (n=931) or IV (n=222) heart failure on stable doses of diuretics, digoxin, and ACE inhibitors, amlodipine had no effect on the primary endpoint of the study which was the combined endpoint of all-cause mortality and cardiac morbidity (as defined by life-threatening arrhythmia, acute myocardial infarction, or hospitalization for worsened heart failure), or on NYHA classification, or symptoms of heart failure. Total combined all-cause mortality and cardiac morbidity events were 222/571 (39%) for patients on amlodipine and 246/583 (42%) for patients on placebo; the cardiac morbid events represented about 25% of the endpoints in the study.

Another study (PRAISE-2) randomized patients with NYHA class III (80%) or IV (20%) heart failure without clinical symptoms or objective evidence of underlying ischemic disease, on stable doses of ACE inhibitor (99%), digitalis (99%) and diuretics (99%), to placebo (n=827) or amlodipine (n=827) and followed them for a mean of 33 months. There was no statistically significant difference between amlodipine and placebo in the primary endpoint of all cause mortality (95% confidence limits from 8% reduction to 29% increase on amlodipine). With amlodipine there were more reports of pulmonary edema.

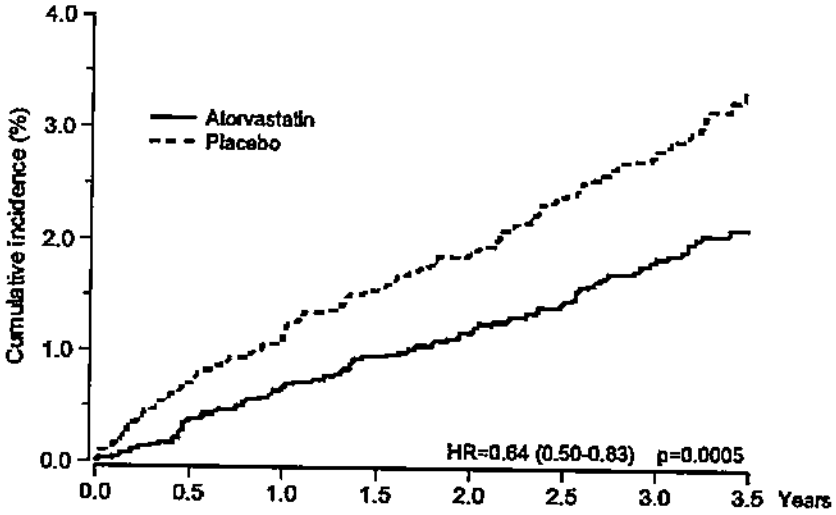
Clinical Studies with Atorvastatin

Prevention of Cardiovascular Disease: In the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), the effect of atorvastatin on fatal and non-fatal coronary heart disease was assessed in 10,305 hypertensive patients 40-80 years of age (mean of 63 years), without a previous myocardial infarction and with TC levels ≤251 mg/dl (6.5 mmol/l). Additionally all patients had at least 3 of the following cardiovascular risk factors: male gender (81.1%), age >55 years (84.5%), smoking (33.2%), diabetes (24.3%), history of CHD in a first-degree relative (26%), TC:HDL >6 (14.3%), peripheral vascular disease (5.1%), left ventricular hypertrophy (14.4%), prior cerebrovascular event (9.8%), specific ECG abnormality (14.3%), proteinuria/albuminuria (62.4%)]. In this double-blind, placebo-controlled study patients were treated with anti-hypertensive therapy (Goal BP <140/90 mm Hg for non-diabetic patients, <130/80 mm Hg for diabetic patients) and allocated to either atorvastatin 10 mg daily (n=5168) or placebo (n=5137), using a covariate adaptive method which took into account the distribution of nine baseline characteristics of patients already enrolled and minimized the imbalance of those characteristics across the groups. Patients were followed for a median duration of 3.3 years.

The effect of 10 mg/day of atorvastatin on lipid levels was similar to that seen in previous clinical trials.

Atorvastatin significantly reduced the rate of coronary events [either fatal coronary heart disease (46 events in the placebo group vs 40 events in the atorvastatin group) or nonfatal MI (108 events in the placebo group vs 60 events in the atorvastatin group)] with a relative risk reduction of 36% [(based on incidences of 1.9% for atorvastatin vs 3.0% for placebo), p=0.0005 (see Figure 3)]. The risk reduction was consistent regardless of age, smoking status, obesity or presence of renal dysfunction. The effect of atorvastatin was seen regardless of baseline LDL levels. Due to the small number of events, results for women were inconclusive.

Figure 3: Effect of Atorvastatin 10 mg/day on Cumulative Incidence of Nonfatal Myocardial Infarction or Coronary Heart Disease Death (in ASCOT-LLA)



Atorvastatin also significantly decreased the relative risk for revascularization procedures by 42%. Although the reduction of fatal and non-fatal strokes did not reach a pre-defined significance level (p=0.01), a favorable trend was observed with a 26% relative risk reduction (incidences of 1.7% for atorvastatin and 2.3% for placebo). There was no significant difference between the treatment groups for death due to cardiovascular causes (p=0.51) or noncardiovascular causes (p=0.17).

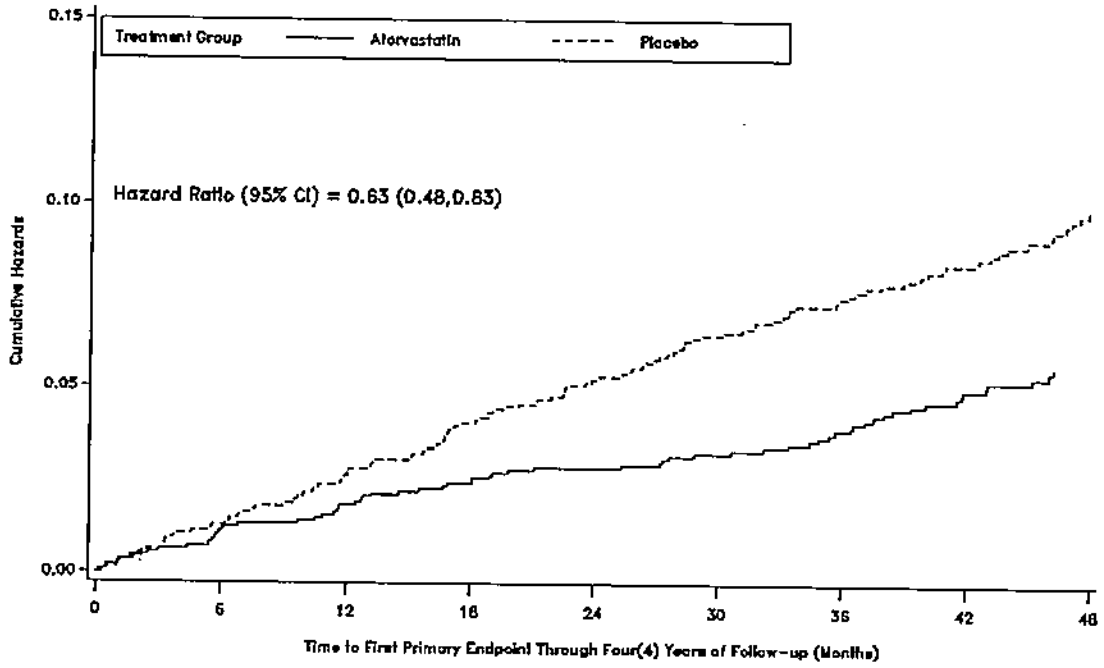
In the Collaborative Atorvastatin Diabetes Study (CARDS), the effect of atorvastatin on cardiovascular disease (CVD) endpoints was assessed in 2838 subjects (94% White, 68% male), ages 40-75 with type 2 diabetes based on WHO criteria, without prior history of cardiovascular disease and with LDL≤ 160 mg/dL and TG ≤600 mg/dL. In addition to diabetes, subjects had 1 or more of the following risk factors: current smoking (23%), hypertension (80%), retinopathy (30%), or microalbuminuria (9%) or macroalbuminuria (3%). No subjects on hemodialysis were enrolled in the study. In this multicenter, placebo-controlled, double-blind clinical trial, subjects were randomly allocated to either atorvastatin 10 mg daily (1429) or placebo (1411) in a 1:1 ratio and were followed for a median duration of 3.9 years. The primary endpoint was the occurrence of any of the major cardiovascular events: myocardial infarction, acute CHD death, unstable angina, coronary revascularization, or stroke. The primary analysis was the time to first occurrence of the primary endpoint.

Baseline characteristics of subjects were: mean age of 62 years, mean HbA_{1c} 7.7%; median LDL-C 120 mg/dL; median TC 207 mg/dL; median TG 151 mg/dL; median HDL-C 52mg/dL.

The effect of atorvastatin 10 mg/day on lipid levels was similar to that seen in previous clinical trials.

Atorvastatin significantly reduced the rate of major cardiovascular events (primary endpoint events) (83 events in the atorvastatin group vs 127 events in the placebo group) with a relative risk reduction of 37%, HR 0.63, 95% CI (0.48, 0.83) (p=0.001) (see Figure 4). An effect of atorvastatin was seen regardless of age, sex, or baseline lipid levels.

Figure 4. Effect of Atorvastatin 10 mg/day on Time to Occurrence of Major Cardiovascular Events (myocardial infarction, acute CHD death, unstable angina, coronary revascularization, or stroke) in CARDS.



Atorvastatin significantly reduced the risk of stroke by 48% (21 events in the atorvastatin group vs 39 events in the placebo group), HR 0.52, 95% CI (0.31, 0.89) (p=0.016) and reduced the risk of MI by 42% (38 events in the atorvastatin group vs 64 events in the placebo group), HR 0.58, 95.1% CI (0.39, 0.86) (p=0.007). There was no significant

difference between the treatment groups for angina, revascularization procedures, and acute CHD death.

There were 61 deaths in the atorvastatin group vs. 82 deaths in the placebo group, (HR 0.73, p=0.059).

Atorvastatin Studies in Hypercholesterolemia (Heterozygous Familial and Nonfamilial) and Mixed Dyslipidemia (Fredrickson Types IIa and IIb*)*: Atorvastatin reduces total-C, LDL-C, VLDL-C, apo B, and TG, and increases HDL-C in patients with hypercholesterolemia and mixed dyslipidemia. Therapeutic response is seen within 2 weeks, and maximum response is usually achieved within 4 weeks and maintained during chronic therapy.

Atorvastatin is effective in a wide variety of patient populations with hypercholesterolemia, with and without hypertriglyceridemia, in men and women, and in the elderly.

In two multicenter, placebo-controlled, dose-response studies in patients with hypercholesterolemia, atorvastatin given as a single dose over 6 weeks significantly reduced total-C, LDL-C, apo B, and TG (pooled results are provided in Table 3).

Table 3. Dose-Response in Patients With Primary Hypercholesterolemia (Adjusted Mean Percent Change From Baseline)[a]

DOSE	N	TC	LDL-C	ApoB	TG	HDL-C	Non-HDL-C/HDL-C
Placebo	21	4	4	3	10	-3	7
10 mg	22	-29	-39	-32	-19	6	-34
20 mg	20	-33	-43	-35	-26	9	-41
40 mg	21	-37	-50	-42	-29	6	-45
80 mg	23	-45	-60	-50	-37	5	-53

[a]Results are pooled from 2 dose-response studies.

In patients with *Fredrickson* Types IIa and IIb hyperlipoproteinemia pooled from 24 controlled trials, the median (25th and 75th percentile) percent changes from baseline in HDL-C for atorvastatin 10, 20, 40, and 80 mg were 6.4 (-1.4, 14), 8.7 (0, 17), 7.8 (0, 16), and 5.1 (-2.7, 15), respectively. Additionally, analysis of the pooled data demonstrated consistent and significant decreases in total-C, LDL-C, TG, total-C/HDL-C, and LDL-C/HDL-C.

In three multicenter, double-blind studies in patients with hypercholesterolemia, atorvastatin was compared to other HMG-CoA reductase inhibitors. After randomization, patients were treated for 16 weeks with either atorvastatin 10 mg per day or a fixed dose of the comparative agent (Table 4).

Table 4. Mean Percent Change From Baseline at Endpoint (Double-Blind, Randomized, Active-Controlled Trials)

Treatment (Daily Dose)	N	Total-C	LDL-C	Apo B	TG	HDL-C	Non-HDL-C/ HDL-C
Study 1							
Atorvastatin 10 mg	707	-27[a]	-36[a]	-28[a]	-17[a]	+7	-37[a]
Lovastatin 20 mg	191	-19	-27	-20	- 6	+7	-28
95% CI for Diff[1]		-9.2, -6.5	-10.7, -7.1	-10.0, -6.5	-15.2, -7.1	-1.7, 2.0	-11.1, -7.1
Study 2							
Atorvastatin 10 mg	222	-25[b]	-35[b]	-27[b]	-17[b]	+6	-36[b]
Pravastatin 20 mg	77	-17	-23	-17	- 9	+8	-28
95% CI for Diff[1]		-10.8, -6.1	-14.5, -8.2	-13.4, -7.4	-14.1, -0.7	-4.9, 1.6	-11.5, -4.1
Study 3							
Atorvastatin 10 mg	132	-29[c]	-37[c]	-34[c]	-23[c]	+7	-39[c]
Simvastatin 10 mg	45	-24	-30	-30	-15	+7	-33
95% CI for Diff[1]		-8.7, -2.7	-10.1, -2.6	-8.0, -1.1	-15.1, -0.7	-4.3, 3.9	-9.6, -1.9

[1] A negative value for the 95% CI for the difference between treatments favors atorvastatin for all except HDL-C, for which a positive value favors atorvastatin. If the range does not include 0, this indicates a statistically significant difference.

[a] Significantly different from lovastatin, ANCOVA, $p \leq 0.05$

[b] Significantly different from pravastatin, ANCOVA, $p \leq 0.05$

[c] Significantly different from simvastatin, ANCOVA, $p \leq 0.05$

The impact on clinical outcomes of the differences in lipid-altering effects between treatments shown in Table 4 is not known. Table 4 does not contain data comparing the effects of atorvastatin 10 mg and higher doses of lovastatin, pravastatin, and simvastatin. The drugs compared in the studies summarized in the table are not necessarily interchangeable.

Atorvastatin Effects in Hypertriglyceridemia (Fredrickson Type IV*)*: The response to atorvastatin in 64 patients with isolated hypertriglyceridemia treated across several clinical trials is shown in the table below. For the atorvastatin-treated patients, median (min, max) baseline TG level was 565 (267-1502).

Table 5. Combined Patients With Isolated Elevated TG: Median (min, max) Percent Changes From Baseline

	Placebo (N=12)	Atorvastatin 10 mg (N=37)	Atorvastatin 20 mg (N=13)	Atorvastatin 80 mg (N=14)
Triglycerides	-12.4 (-36.6, 82.7)	-41.0 (-76.2, 49.4)	-38.7 (-62.7, 29.5)	-51.8 (-82.8, 41.3)
Total-C	-2.3 (-15.5, 24.4)	-28.2 (-44.9, -6.8)	-34.9 (-49.6, -15.2)	-44.4 (-63.5, -3.8)
LDL-C	3.6 (-31.3, 31.6)	-26.5 (-57.7, 9.8)	-30.4 (-53.9, 0.3)	-40.5 (-60.6, -13.8)
HDL-C	3.8 (-18.6, 13.4)	13.8 (-9.7, 61.5)	11.0 (-3.2, 25.2)	7.5 (-10.8, 37.2)
VLDL-C	-1.0 (-31.9, 53.2)	-48.8 (-85.8, 57.3)	-44.6 (-62.2, -10.8)	-62.0 (-88.2, 37.6)
non-HDL-C	-2.8 (-17.6, 30.0)	-33.0 (-52.1, -13.3)	-42.7 (-53.7, -17.4)	-51.5 (-72.9, -4.3)

Atorvastatin Effects in Dysbetalipoproteinemia (Fredrickson Type III*)*: The results of an open-label crossover study of atorvastatin in 16 patients (genotypes: 14 apo E2/E2 and 2 apo E3/E2) with dysbetalipoproteinemia (*Fredrickson* Type III) are shown in the table below.

Table 6. Open-Label Crossover Study of 16 Patients With Dysbetalipoproteinemia (*Fredrickson* Type III)

	Median (min, max) at Baseline (mg/dL)	Median % Change (min, max)	
		Atorvastatin 10 mg	Atorvastatin 80 mg
Total-C	442 (225, 1320)	-37 (-85, 17)	-58 (-90, -31)
Triglycerides	678 (273, 5990)	-39 (-92, -8)	-53 (-95, -30)
IDL-C + VLDL-C	215 (111, 613)	-32 (-76, 9)	-63 (-90, -8)
non-HDL-C	411 (218, 1272)	-43 (-87, -19)	-64 (-92, -36)

Atorvastatin Effects in Homozygous Familial Hypercholesterolemia: In a study without a concurrent control group, 29 patients ages 6 to 37 years with homozygous FH received maximum daily doses of 20 to 80 mg of atorvastatin. The mean LDL-C reduction in this study was 18%. Twenty-five patients with a reduction in LDL-C had a mean response of 20% (range of 7% to 53%, median of 24%); the remaining 4 patients had 7% to 24% increases in LDL-C. Five of the 29 patients had absent LDL-receptor function. Of these, 2 patients also had a portacaval shunt and had no significant reduction in LDL-C. The remaining 3 receptor-negative patients had a mean LDL-C reduction of 22%.

Atorvastatin Effects in Heterozygous Familial Hypercholesterolemic Pediatric Patients: In a double-blind, placebo-controlled study followed by an open-label phase, 187 boys and postmenarchal girls 10-17 years of age (mean age 14.1 years) with heterozygous FH or severe hypercholesterolemia were randomized to atorvastatin (n=140) or placebo (n=47) for 26 weeks and then all received atorvastatin for 26 weeks. Inclusion in the study required 1) a baseline LDL-C level ≥ 190 mg/dL or 2) a baseline LDL-C ≥ 160 mg/dL and positive family history of FH or documented premature cardiovascular disease in a first- or second-degree relative. The mean baseline LDL-C value was 218.6 mg/dL (range: 138.5-385.0 mg/dL) in the atorvastatin group compared to 230.0 mg/dL (range: 160.0-324.5 mg/dL) in placebo group. The dosage of atorvastatin (once daily) was 10 mg for the first 4 weeks and up-titrated to 20 mg if the LDL-C level was > 130 mg/dL. The number of atorvastatin-treated patients who required up-titration to 20 mg after Week 4 during the double-blind phase was 80 (57.1%).

Atorvastatin significantly decreased plasma levels of total-C, LDL-C, triglycerides, and apolipoprotein B during the 26 week double-blind phase (see Table 7).

Table 7. Lipid-altering Effects of Atorvastatin in Adolescent Boys and Girls with Heterozygous Familial Hypercholesterolemia or Severe Hypercholesterolemia (Mean Percent Change from Baseline at Endpoint in Intention-to-Treat Population)

DOSAGE	N	Total-C	LDL-C	HDL-C	TG	Apolipoprotein B
Placebo	47	-1.5	-0.4	-1.9	1.0	0.7
Atorvastatin	140	-31.4	-39.6	2.8	-12.0	-34.0

The mean achieved LDL-C value was 130.7 mg/dL (range: 70.0-242.0 mg/dL) in the atorvastatin group compared to 228.5 mg/dL (range: 152.0-385.0 mg/dL) in the placebo group during the 26 week double-blind phase.

The safety and efficacy of atorvastatin doses above 20 mg have not been studied in controlled trials in children. The long-term efficacy of atorvastatin therapy in childhood to reduce morbidity and mortality in adulthood has not been established.

Clinical Study of Combined Amlodipine and Atorvastatin in Patients with Hypertension and Dyslipidemia

In a double-blind, placebo-controlled study, a total of 1660 patients with co-morbid hypertension and dyslipidemia received once daily treatment with eight dose combinations of amlodipine and atorvastatin (5/10, 10/10, 5/20, 10/20, 5/40, 10/40, 5/80, or 10/80 mg), amlodipine alone (5 mg or 10 mg), atorvastatin alone (10 mg, 20 mg, 40 mg, or 80 mg) or placebo. In addition to concomitant hypertension and dyslipidemia, 15% of the patients had diabetes mellitus, 22% were smokers and 14% had a positive family history of cardiovascular disease. At eight weeks, all eight combination-treatment groups of amlodipine and atorvastatin demonstrated statistically significant dose-related reductions in systolic blood pressure (SBP), diastolic blood pressure (DBP) and LDL-C compared to placebo, with no overall modification of effect of either component on SBP, DBP and LDL-C (Table 8).

Table 8. Efficacy in Terms of Reduction in Blood Pressure and LDL-C

Efficacy of the Combined Treatments in Reducing Systolic BP

Parameter / Analysis		ATO 0 mg	ATO 10 mg	ATO 20 mg	ATO 40 mg	ATO 80 mg
AML 0 mg	Mean change (mmHg)	-3.0	-4.5	-6.2	-6.2	-6.4
	Difference versus placebo (mmHg)	-	-1.5	-3.2	-3.2	-3.4
AML 5 mg	Mean change (mmHg)	-12.8	-13.7	-15.3	-12.7	-12.2
	Difference versus placebo (mmHg)	-9.8	-10.7	-12.3	-9.7	-9.2
AML 10 mg	Mean change (mmHg)	-16.2	-15.9	-16.1	-16.3	-17.6
	Difference versus placebo (mmHg)	-13.2	-12.9	-13.1	-13.3	-14.6

Efficacy of the Combined Treatments in Reducing Diastolic BP

Parameter / Analysis		ATO 0 mg	ATO 10 mg	ATO 20 mg	ATO 40 mg	ATO 80 mg
AML 0 mg	Mean change (mmHg)	-3.3	-4.1	-3.9	-5.1	-4.1
	Difference versus placebo (mmHg)	-	-0.8	-0.6	-1.8	-0.8
AML 5 mg	Mean change (mmHg)	-7.6	-8.2	-9.4	-7.3	-8.4
	Difference versus placebo (mmHg)	-4.3	-4.9	-6.1	-4.0	-5.1
AML 10 mg	Mean change (mmHg)	-10.4	-9.1	-10.6	-9.8	-11.1
	Difference versus placebo (mmHg)	-7.1	-5.8	-7.3	-6.5	-7.8

Efficacy of the Combined Treatments in Reducing LDL-C (% change)

Parameter / Analysis		ATO 0 mg	ATO 10 mg	ATO 20 mg	ATO 40 mg	ATO 80 mg
AML 0 mg	Mean % change	-1.1	-33.4	-39.5	-43.1	-47.2
AML 5 mg	Mean % change	-0.1	-38.7	-42.3	-44.9	-48.4
AML 10 mg	Mean % change	-2.5	-36.6	-38.6	-43.2	-49.1

INDICATIONS AND USAGE

CADUET (amlodipine and atorvastatin) is indicated in patients for whom treatment with both amlodipine and atorvastatin is appropriate.

Amlodipine

1. ***Hypertension*:** Amlodipine is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents;
2. ***Coronary Artery Disease (CAD)***
   Chronic Stable Angina: Amlodipine is indicated for the treatment of chronic stable angina. Amlodipine may be used alone or in combination with other antianginal or antihypertensive agents;
   Vasospastic Angina (Prinzmetal's or Variant Angina): Amlodipine is indicated for the treatment of confirmed or suspected vasospastic angina. Amlodipine may be used as monotherapy or in combination with other antianginal drugs.
   Angiographically Documented CAD: In patients with recently documented CAD by angiography and without heart failure or an ejection fraction <40%, amlodipine is indicated to reduce the risk of hospitalization due to angina and to reduce the risk of a coronary revascularization procedure.

AND

Atorvastatin

1. ***Prevention of Cardiovascular Disease:*** In adult patients without clinically evident coronary heart disease, but with multiple risk factors for coronary heart disease such as age, smoking, hypertension, low HDL-C, or a family history of early coronary heart disease, atorvastatin is indicated to:
   - Reduce the risk of myocardial infarction
   - Reduce the risk of stroke
   - Reduce the risk for revascularization procedures and angina

   In patients with type 2 diabetes, and without clinically evident coronary heart disease, but with multiple risk factors for coronary heart disease such as retinopathy, albuminuria, smoking, or hypertension, LIPITOR is indicated to:
   - Reduce the risk of myocardial infarction
   - Reduce the risk of stroke;
2. ***Heterozygous Familial and Nonfamilial Hypercholesterolemia*:** Atorvastatin is indicated as an adjunct to diet to reduce elevated total-C, LDL-C, apo B, and TG levels and to increase HDL-C in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (*Fredrickson* Types IIa and IIb);
3. ***Elevated Serum TG Levels*:** Atorvastatin is indicated as an adjunct to diet for the treatment of patients with elevated serum TG levels (*Fredrickson* Type IV);
4. ***Primary Dysbetalipoproteinemia*:** Atorvastatin is indicated for the treatment of patients with primary dysbetalipoproteinemia (*Fredrickson* Type III) who do not respond adequately to diet;
5. ***Homozygous Familial Hypercholesterolemia*:** Atorvastatin is indicated to reduce total-C and LDL-C in patients with homozygous familial hypercholesterolemia as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable;
6. ***Pediatric Patients*:** Atorvastatin is indicated as an adjunct to diet to reduce total-C, LDL-C, and apo B levels in boys and postmenarchal girls, 10 to 17 years of age, with heterozygous familial hypercholesterolemia if after an adequate trial of diet therapy the following findings are present:

   a. LDL-C remains ≥ 190 mg/dL or
   b. LDL-C remains ≥ 160 mg/dL and:
      - there is a positive family history of premature cardiovascular disease or
      - two or more other CVD risk factors are present in the pediatric patients.

Therapy with lipid-altering agents should be a component of multiple-risk-factor intervention in individuals at increased risk for atherosclerotic vascular disease due to hypercholesterolemia. Lipid-altering agents should be used, in addition to a diet restricted in saturated fat and cholesterol, only when the response to diet and other nonpharmacological measures has been inadequate (see *National Cholesterol Education Program (NCEP) Guidelines,* summarized in Table 9).

Table 9. NCEP Treatment Guidelines: LDL-C Goals and Cutpoints for Therapeutic Lifestyle Changes and Drug Therapy in Different Risk Categories

Risk Category	LDL-C Goal (mg/dL)	LDL-C Level at Which to Initiate Therapeutic Lifestyle Changes (mg/dL)	LDL-C Level at Which to Consider Drug Therapy (mg/dL)
CHD [a] or CHD risk equivalents (10-year risk >20%)	<100	≥100	≥130 (100-129: drug optional) [b]
2+ Risk Factors (10-year risk ≤20%)	<130	≥130	10-year risk 10%-20%: ≥130 10-year risk <10%: ≥ 160
0-1 Risk Factor [c]	<160	≥160	≥190 (160-189: LDL-lowering drug optional)

[a] CHD, coronary heart disease
[b] Some authorities recommend use of LDL-lowering drugs in this category if an LDL-C level of < 100 mg/dL cannot be achieved by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and HDL-C, e.g., nicotinic acid or fibrate. Clinical judgment also may call for deferring drug therapy in this subcategory.
[c] Almost all people with 0-1 risk factor have 10-year risk <10%; thus, 10-year risk assessment in people with 0-1 risk factor is not necessary.

After the LDL-C goal has been achieved, if the TG is still ≥ 200 mg/dL, non-HDL-C (total-C minus HDL-C) becomes a secondary target of therapy. Non-HDL-C goals are set 30 mg/dL higher than LDL-C goals for each risk category.

Prior to initiating therapy with atorvastatin, secondary causes for hypercholesterolemia (e.g., poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemias, obstructive liver disease, other drug therapy, and alcoholism) should be excluded, and a lipid profile performed to measure total-C, LDL-C, HDL-C, and TG. For patients with TG <400 mg/dL (<4.5 mmol/L), LDL-C can be estimated using the following equation: LDL-C = total-C - (0.20 x [TG] + HDL-C). For TG levels >400 mg/dL (>4.5 mmol/L), this equation is less accurate and LDL-C concentrations should be determined by ultracentrifugation.

The antidyslipidemic component of CADUET has not been studied in conditions where the major lipoprotein abnormality is elevation of chylomicrons (*Fredrickson* Types I and V).

The NCEP classification of cholesterol levels in pediatric patients with a familial history of hypercholesterolemia or premature cardiovascular disease is summarized below:

Table 10. NCEP Classification of Cholesterol Levels in Pediatric Patients

Category	Total-C (mg/dL)	LDL-C (mg/dL)
Acceptable	<170	<110
Borderline	170-199	110-129
High	≥200	≥130

CONTRAINDICATIONS

CADUET contains atorvastatin and is therefore contraindicated in patients with active liver disease or unexplained persistent elevations of serum transaminases.

CADUET is contraindicated in patients with known hypersensitivity to any component of this medication.

Pregnancy and Lactation

Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). Since HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they may cause fetal harm when administered to pregnant women. Therefore, HMG-CoA reductase inhibitors are contraindicated during pregnancy and in nursing mothers. CADUET, WHICH INCLUDES ATORVASTATIN, SHOULD BE ADMINISTERED TO WOMEN OF CHILDBEARING AGE ONLY WHEN SUCH PATIENTS ARE HIGHLY UNLIKELY TO CONCEIVE AND HAVE BEEN INFORMED OF THE POTENTIAL HAZARDS. If the patient becomes pregnant while taking this drug, therapy should be discontinued and the patient apprised of the potential hazard to the fetus.

WARNINGS

Increased Angina and/or Myocardial Infarction

Rarely, patients, particularly those with severe obstructive coronary artery disease, have developed documented increased frequency, duration and/or severity of angina or acute myocardial infarction on starting calcium channel blocker therapy or at the time of dosage increase. The mechanism of this effect has not been elucidated.

Liver Dysfunction

HMG-CoA reductase inhibitors, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. **Persistent elevations (>3 times the upper limit of normal [ULN] occurring on 2 or more occasions) in serum transaminases occurred in 0.7% of patients who received atorvastatin in clinical trials. The incidence of these abnormalities was 0.2%, 0.2%, 0.6%, and 2.3% for 10, 20, 40, and 80 mg, respectively.**

In clinical trials in patients taking atorvastatin the following has been observed. One patient in clinical trials developed jaundice. Increases in liver function tests (LFT) in other patients

were not associated with jaundice or other clinical signs or symptoms. Upon dose reduction, drug interruption, or discontinuation, transaminase levels returned to or near pretreatment levels without sequelae. Eighteen of 30 patients, with persistent LFT elevations continued treatment with a reduced dose of atorvastatin.

It is recommended that liver function tests be performed prior to and at 12 weeks following both the initiation of therapy and any elevation of dose, and periodically (e.g., semiannually) thereafter. Liver enzyme changes generally occur in the first 3 months of treatment with atorvastatin. Patients who develop increased transaminase levels should be monitored until the abnormalities resolve. Should an increase in ALT or AST of >3 times ULN persist, reduction of dose or withdrawal of CADUET is recommended.

CADUET should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease. Active liver disease or unexplained persistent transaminase elevations are contraindications to the use of CADUET (see **CONTRAINDICATIONS**).

Skeletal Muscle
Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with the atorvastatin component of CADUET and with other drugs in the HMG-CoA reductase inhibitor class.

Uncomplicated myalgia has been reported in atorvastatin-treated patients (see **ADVERSE REACTIONS**). Myopathy, defined as muscle aches or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values >10 times ULN, should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. CADUET therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected.

The risk of myopathy during treatment with drugs in the HMG-CoA reductase inhibitor class is increased with concurrent administration of cyclosporine, fibric acid derivatives, erythromycin, niacin, or azole antifungals. Physicians considering combined therapy with CADUET and fibric acid derivatives, erythromycin, immunosuppressive drugs, azole antifungals, or lipid-lowering doses of niacin should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs or symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Periodic creatine phosphokinase (CPK) determinations may be considered in such situations, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy.

In patients taking CADUET, therapy should be temporarily withheld or discontinued in any patient with an acute, serious condition suggestive of a myopathy or having a risk factor predisposing to the development of renal failure secondary to

rhabdomyolysis (e.g., severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders, and uncontrolled seizures).

PRECAUTIONS

General

Since the vasodilation induced by the amlodipine component of CADUET is gradual in onset, acute hypotension has rarely been reported after oral administration of amlodipine. Nonetheless, caution should be exercised when administering CADUET as with any other peripheral vasodilator particularly in patients with severe aortic stenosis.

Before instituting therapy with CADUET, an attempt should be made to control hypercholesterolemia with appropriate diet, exercise, and weight reduction in obese patients, and to treat other underlying medical problems (see **INDICATIONS AND USAGE**).

Use in Patients with Congestive Heart Failure

In general, calcium channel blockers should be used with caution in patients with heart failure. The amlodipine component of CADUET (5-10 mg per day) has been studied in a placebo-controlled trial of 1153 patients with NYHA Class III or IV heart failure (see **CLINICAL PHARMACOLOGY**) on stable doses of ACE inhibitor, digoxin, and diuretics. Follow-up was at least 6 months, with a mean of about 14 months. There was no overall adverse effect on survival or cardiac morbidity (as defined by life-threatening arrhythmia, acute myocardial infarction, or hospitalization for worsened heart failure). Amlodipine has been compared to placebo in four 8-12 week studies of patients with NYHA class II/III heart failure, involving a total of 697 patients. In these studies, there was no evidence of worsened heart failure based on measures of exercise tolerance, NYHA classification, symptoms, or LVEF.

Beta-Blocker Withdrawal

The amlodipine component of CADUET is not a beta-blocker and therefore gives no protection against the dangers of abrupt beta-blocker withdrawal; any such withdrawal should be by gradual reduction of the dose of beta-blocker.

Endocrine Function

HMG-CoA reductase inhibitors, such as the atorvastatin component of CADUET interfere with cholesterol synthesis and theoretically might blunt adrenal and/or gonadal steroid production. Clinical studies have shown that atorvastatin does not reduce basal plasma cortisol concentration or impair adrenal reserve. The effects of HMG-CoA reductase inhibitors on male fertility have not been studied in adequate numbers of patients. The effects, if any, on the pituitary-gonadal axis in premenopausal women are unknown. Caution should be exercised if an HMG-CoA reductase inhibitor is administered

concomitantly with drugs that may decrease the levels or activity of endogenous steroid hormones, such as ketoconazole, spironolactone, and cimetidine.

CNS Toxicity

Studies with atorvastatin: Brain hemorrhage was seen in a female dog treated with atorvastatin calcium for 3 months at a dose equivalent to 120 mg atorvastatin/kg/day. Brain hemorrhage and optic nerve vacuolation were seen in another female dog that was sacrificed in moribund condition after 11 weeks of escalating doses of atorvastatin calcium equivalent to up to 280 mg atorvastatin/kg/day. The 120 mg/kg dose of atorvastatin resulted in a systemic exposure approximately 16 times the human plasma area-under-the-curve (AUC, 0-24 hours) based on the maximum human dose of 80 mg/day. A single tonic convulsion was seen in each of 2 male dogs (one treated with atorvastatin calcium at a dose equivalent to 10 mg atorvastatin/kg/day and one at a dose equivalent to 120 mg atorvastatin/kg/day) in a 2-year study. No CNS lesions have been observed in mice after chronic treatment for up to 2 years at doses of atorvastatin calcium equivalent to up to 400 mg atorvastatin/kg/day or in rats at doses equivalent to up to 100 mg atorvastatin/kg/day. These doses were 6 to 11 times (mouse) and 8 to 16 times (rat) the human AUC (0-24) based on the maximum recommended human dose of 80 mg atorvastatin/day.

CNS vascular lesions, characterized by perivascular hemorrhages, edema, and mononuclear cell infiltration of perivascular spaces, have been observed in dogs treated with other members of the HMG-CoA reductase class. A chemically similar drug in this class produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion at a dose that produced plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose.

Information for Patients

Due to the risk of myopathy with drugs of the HMG-CoA reductase class, to which the atorvastatin component of CADUET belongs, patients should be advised to report promptly unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever.

Drug Interactions

Data from a drug-drug interaction study involving 10 mg of amlodipine and 80 mg of atorvastatin in healthy subjects indicate that the pharmacokinetics of amlodipine are not altered when the drugs are coadministered. The effect of amlodipine on the pharmacokinetics of atorvastatin showed no effect on the Cmax: 91% (90% confidence interval: 80 to 103%), but the AUC of atorvastatin increased by 18% (90% confidence interval: 109 to 127%) in the presence of amlodipine.

No drug interaction studies have been conducted with CADUET and other drugs, although studies have been conducted in the individual amlodipine and atorvastatin components, as described below:

Studies with Amlodipine:

In vitro data in human plasma indicate that amlodipine has no effect on the protein binding of drugs tested (digoxin, phenytoin, warfarin, and indomethacin).

Cimetidine: Co-administration of amlodipine with cimetidine did not alter the pharmacokinetics of amlodipine.

Maalox® (antacid): Co-administration of the antacid Maalox with a single dose of amlodipine had no significant effect on the pharmacokinetics of amlodipine.

Sildenafil: A single 100 mg dose of sildenafil (Viagra®) in subjects with essential hypertension had no effect on the pharmacokinetic parameters of amlodipine. When amlodipine and sildenafil were used in combination, each agent independently exerted its own blood pressure lowering effect.

Digoxin: Co-administration of amlodipine with digoxin did not change serum digoxin levels or digoxin renal clearance in normal volunteers.

Ethanol (alcohol): Single and multiple 10 mg doses of amlodipine had no significant effect on the pharmacokinetics of ethanol.

Warfarin: Co-administration of amlodipine with warfarin did not change the warfarin prothrombin response time.

In clinical trials, amlodipine has been safely administered with thiazide diuretics, beta-blockers, angiotensin-converting enzyme inhibitors, long-acting nitrates, sublingual nitroglycerin, digoxin, warfarin, non-steroidal anti-inflammatory drugs, antibiotics, and oral hypoglycemic drugs.

Studies with Atorvastatin:

The risk of myopathy during treatment with drugs of the HMG-CoA reductase class is increased with concurrent administration of cyclosporine, fibric acid derivatives, niacin (nicotinic acid), erythromycin, or azole antifungals (see **WARNINGS, Skeletal Muscle**).

Antacid: When atorvastatin and Maalox TC suspension were coadministered, plasma concentrations of atorvastatin decreased approximately 35%. However, LDL-C reduction was not altered.

Antipyrine: Because atorvastatin does not affect the pharmacokinetics of antipyrine, interactions with other drugs metabolized via the same cytochrome isozymes are not expected.

Colestipol: Plasma concentrations of atorvastatin decreased approximately 25% when colestipol and atorvastatin were coadministered. However, LDL-C reduction was greater when atorvastatin and colestipol were coadministered than when either drug was given alone.

Cimetidine: Atorvastatin plasma concentrations and LDL-C reduction were not altered by coadministration of cimetidine.

Digoxin: When multiple doses of atorvastatin and digoxin were coadministered, steady-state plasma digoxin concentrations increased by approximately 20%. Patients taking digoxin should be monitored appropriately.

Erythromycin: In healthy individuals, plasma concentrations of atorvastatin increased approximately 40% with coadministration of atorvastatin and erythromycin, a known inhibitor of cytochrome P450 3A4 (see **WARNINGS, Skeletal Muscle**).

Oral Contraceptives: Coadministration of atorvastatin and an oral contraceptive increased AUC values for norethindrone and ethinyl estradiol by approximately 30% and 20%. These increases should be considered when selecting an oral contraceptive for a woman taking CADUET.

Warfarin: Atorvastatin had no clinically significant effect on prothrombin time when administered to patients receiving chronic warfarin treatment.

Drug/Laboratory Test Interactions
None known.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies with amlodipine: Rats and mice treated with amlodipine maleate in the diet for up to two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 mg amlodipine/kg/day, showed no evidence of a carcinogenic effect of the drug. For the mouse, the highest dose was, on a mg/m^2 basis, similar to the maximum recommended human dose of 10 mg amlodipine/day*. For the rat, the highest dose level was, on a mg/m^2 basis, about twice the maximum recommended human dose*.

Mutagenicity studies conducted with amlodipine maleate revealed no drug related effects at either the gene or chromosome levels.

There was no effect on the fertility of rats treated orally with amlodipine maleate (males for 64 days and females for 14 days prior to mating) at doses up to 10 mg amlodipine/kg/day (8 times* the maximum recommended human dose of 10 mg/day on a mg/m^2 basis).

*Based on patient weight of 50 kg.

Studies with atorvastatin: In a 2-year carcinogenicity study with atorvastatin calcium in rats at dose levels equivalent to 10, 30, and 100 mg atorvastatin/kg/day, 2 rare tumors were found in muscle in high-dose females: in one, there was a rhabdomyosarcoma and, in another, there was a fibrosarcoma. This dose represents a plasma AUC (0-24) value of approximately 16 times the mean human plasma drug exposure after an 80 mg oral dose.

A 2-year carcinogenicity study in mice given atorvastatin calcium at dose levels equivalent to 100, 200, and 400 mg atorvastatin/kg/day resulted in a significant increase in liver adenomas in high-dose males and liver carcinomas in high-dose females. These findings occurred at plasma AUC (0-24) values of approximately 6 times the mean human plasma drug exposure after an 80 mg oral dose.

In vitro, atorvastatin was not mutagenic or clastogenic in the following tests with and without metabolic activation: the Ames test with *Salmonella typhimurium* and *Escherichia coli*, the HGPRT forward mutation assay in Chinese hamster lung cells, and the chromosomal aberration assay in Chinese hamster lung cells. Atorvastatin was negative in the *in vivo* mouse micronucleus test.

There were no effects on fertility when rats were given atorvastatin calcium at doses equivalent to up to 175 mg atorvastatin/kg/day (15 times the human exposure). There was aplasia and aspermia in the epididymides of 2 of 10 rats treated with atorvastatin calcium at a dose equivalent to 100 mg atorvastatin/kg/day for 3 months (16 times the human AUC at the 80 mg dose); testis weights were significantly lower at 30 and 100 mg/kg/day and epididymal weight was lower at 100 mg/kg/day. Male rats given the equivalent of 100 mg atorvastatin/kg/day for 11 weeks prior to mating had decreased sperm motility, spermatid head concentration, and increased abnormal sperm. Atorvastatin caused no adverse effects on semen parameters, or reproductive organ histopathology in dogs given doses of atorvastatin calcium equivalent to 10, 40, or 120 mg atorvastatin/kg/day for two years.

Pregnancy
Pregnancy Category X (see CONTRAINDICATIONS)

Safety in pregnant women has not been established with CADUET. CADUET should be administered to women of child-bearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the woman becomes pregnant while taking CADUET, it should be discontinued and the patient advised again as to the potential hazards to the fetus.

Studies with amlodipine: No evidence of teratogenicity or other embryo/fetal toxicity was found when pregnant rats and rabbits were treated orally with amlodipine maleate at doses up to 10 mg amlodipine/kg/day (respectively 8 times* and 23 times* the maximum recommended human dose of 10 mg/day on a mg/m^2 basis) during their respective periods of major organogenesis. However, litter size was significantly decreased (by about 50%) and the number of intrauterine deaths was significantly increased (about 5-fold) in rats receiving amlodipine maleate at 10 mg amlodipine/kg/day for 14 days before mating and throughout mating and gestation. Amlodipine maleate has been shown to prolong both the gestation period and the duration of labor in rats at this dose. There are no adequate and well-controlled studies in pregnant women.

*Based on patient weight of 50 kg.

Studies with atorvastatin: Atorvastatin crosses the rat placenta and reaches a level in fetal liver equivalent to that of maternal plasma. Atorvastatin was not teratogenic in rats at doses of atorvastatin calcium equivalent to up to 300 mg atorvastatin/kg/day or in rabbits at doses of atorvastatin calcium equivalent to up to 100 mg atorvastatin/kg/day. These doses resulted in multiples of about 30 times (rat) or 20 times (rabbit) the human exposure based on surface area (mg/m^2).

In a study in rats given atorvastatin calcium at doses equivalent to 20, 100, or 225 mg atorvastatin/kg/day, from gestation day 7 through to lactation day 21 (weaning), there was decreased pup survival at birth, neonate, weaning, and maturity for pups of mothers dosed with 225 mg/kg/day. Body weight was decreased on days 4 and 21 for pups of mothers dosed at 100 mg/kg/day; pup body weight was decreased at birth and at days 4, 21, and 91 at 225 mg/kg/day. Pup development was delayed (rotorod performance at 100 mg/kg/day and acoustic startle at 225 mg/kg/day; pinnae detachment and eye opening at 225 mg/kg/day). These doses of atorvastatin correspond to 6 times (100 mg/kg) and 22 times (225 mg/kg) the human AUC at 80 mg/day.

Rare reports of congenital anomalies have been received following intrauterine exposure to HMG-CoA reductase inhibitors. There has been one report of severe congenital bony deformity, tracheo-esophageal fistula, and anal atresia (VATER association) in a baby born to a woman who took lovastatin with dextroamphetamine sulfate during the first trimester of pregnancy.

Labor and Delivery

No studies have been conducted in pregnant women on the effect of CADUET, amlodipine or atorvastatin on the mother or the fetus during labor or delivery, or on the duration of labor or delivery. Amlodipine has been shown to prolong the duration of labor in rats.

Nursing Mothers

It is not known whether the amlodipine component of CADUET is excreted in human milk. Nursing rat pups taking atorvastatin had plasma and liver drug levels of 50% and 40%, respectively, of that in their mother's milk. Because of the potential for adverse reactions in nursing infants, women taking CADUET should not breast-feed (see **CONTRAINDICATIONS**).

Pediatric Use

There have been no studies conducted to determine the safety or effectiveness of CADUET in pediatric populations.

Studies with amlodipine: The effect of amlodipine on blood pressure in patients less than 6 years of age is not known.

Studies with atorvastatin: Safety and effectiveness in patients 10-17 years of age with heterozygous familial hypercholesterolemia have been evaluated in controlled clinical trials of 6 months duration in adolescent boys and postmenarchal girls. Patients treated with atorvastatin had an adverse experience profile generally similar to that of patients treated with placebo, the most common adverse experiences observed in both groups, regardless of causality assessment, were infections. **Doses greater than 20 mg have not been studied in this patient population.** In this limited controlled study, there was no detectable effect on growth or sexual maturation in boys or on menstrual cycle length in girls. See **CLINICAL PHARMACOLOGY, Clinical Studies** section; **ADVERSE REACTIONS,** *Pediatric Patients;* and **DOSAGE AND ADMINISTRATION,** *Pediatric Patients (10-17 years of age) with Heterozygous Familial Hypercholesterolemia.* Adolescent females should be counseled on appropriate contraceptive methods while on atorvastatin therapy (see **CONTRAINDICATIONS** and **PRECAUTIONS, Pregnancy**). **Atorvastatin has not been studied in controlled clinical trials involving pre-pubertal patients or patients younger than 10 years of age.**

Clinical efficacy with doses of atorvastatin up to 80 mg/day for 1 year have been evaluated in an uncontrolled study of patients with homozygous FH including 8 pediatric patients. See **CLINICAL PHARMACOLOGY, Clinical Studies,** *Atorvastatin Effects in Homozygous Familial Hypercholesterolemia.*

Geriatric Use

There have been no studies conducted to determine the safety or effectiveness of CADUET in geriatric populations.

In studies with amlodipine: Clinical studies of amlodipine did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection of the amlodipine component of CADUET for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. Elderly patients have decreased clearance of amlodipine with a resulting increase of AUC of approximately 40-60%, and a lower initial dose may be required (see **DOSAGE AND ADMINISTRATION**).

In studies with atorvastatin: The safety and efficacy of atorvastatin (10-80 mg) in the geriatric population (≥65 years of age) was evaluated in the ACCESS study. In this 54-week open-label trial 1,958 patients initiated therapy with atorvastatin calcium 10 mg. Of these, 835 were elderly (≥65 years) and 1,123 were non-elderly. The mean change in LDL-C from baseline after 6 weeks of treatment with atorvastatin calcium 10 mg was –38.2% in the elderly patients versus –34.6% in the non-elderly group.

The rates of discontinuation in patients on atorvastatin due to adverse events were similar between the two age groups. There were no differences in clinically relevant laboratory abnormalities between the age groups.

In studies with Atorvastatin

Use in Patients with Recent Stroke or TIA

In a post-hoc analysis of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study where LIPITOR 80 mg vs placebo was administered in 4,731 subjects without CHD who had a stroke or TIA within the preceding 6 months, a higher incidence of hemorrhagic stroke was seen in the LIPITOR 80 mg group compared to placebo. Subjects with hemorrhagic stroke on study entry appeared to be at increased risk for hemorrhagic stroke.

ADVERSE REACTIONS

CADUET

CADUET (amlodipine besylate/atorvastatin calcium) has been evaluated for safety in 1092 patients in double-blind placebo controlled studies treated for co-morbid hypertension and dyslipidemia. In general, treatment with CADUET was well tolerated. For the most part, adverse experiences have been mild or moderate in severity. In clinical trials with CADUET, no adverse experiences peculiar to this combination have been observed. Adverse experiences are similar in terms of nature, severity, and frequency to those reported previously with amlodipine and atorvastatin.

The following information is based on the clinical experience with amlodipine and atorvastatin.

The Amlodipine Component of CADUET

Amlodipine has been evaluated for safety in more than 11,000 patients in U.S. and foreign clinical trials. In general, treatment with amlodipine was well tolerated at doses up to 10 mg daily. Most adverse reactions reported during therapy with amlodipine were of mild or moderate severity. In controlled clinical trials directly comparing amlodipine (N=1730) in doses up to 10 mg to placebo (N=1250), discontinuation of amlodipine due to adverse reactions was required in only about 1.5% of patients and was not significantly different from placebo (about 1%). The most common side effects are headache and edema. The incidence (%) of side effects which occurred in a dose related manner are as follows:

Adverse Event	amlodipine			
	2.5 mg N=275	5.0 mg N=296	10.0 mg N=268	Placebo N=520
Edema	1.8	3.0	10.8	0.6
Dizziness	1.1	3.4	3.4	1.5

Flushing	0.7	1.4	2.6	0.0
Palpitations	0.7	1.4	4.5	0.6

Other adverse experiences which were not clearly dose related but which were reported with an incidence greater than 1.0% in placebo-controlled clinical trials include the following:

Placebo-Controlled Studies

Adverse Event	amlodipine (%) (N=1730)	Placebo (%) (N=1250)
Headache	7.3	7.8
Fatigue	4.5	2.8
Nausea	2.9	1.9
Abdominal Pain	1.6	0.3
Somnolence	1.4	0.6

For several adverse experiences that appear to be drug and dose related, there was a greater incidence in women than men associated with amlodipine treatment as shown in the following table:

Adverse Event	amlodipine		Placebo	
	M=% (N=1218)	F=% (N=512)	M=% (N=914)	F=% (N=336)
Edema	5.6	14.6	1.4	5.1
Flushing	1.5	4.5	0.3	0.9
Palpitations	1.4	3.3	0.9	0.9
Somnolence	1.3	1.6	0.8	0.3

The following events occurred in <1% but >0.1% of patients treated with amlodipine in controlled clinical trials or under conditions of open trials or marketing experience where a causal relationship is uncertain; they are listed to alert the physician to a possible relationship:

Cardiovascular: arrhythmia (including ventricular tachycardia and atrial fibrillation), bradycardia, chest pain, hypotension, peripheral ischemia, syncope, tachycardia, postural dizziness, postural hypotension, vasculitis.

Central and Peripheral Nervous System: hypoesthesia, neuropathy peripheral, paresthesia, tremor, vertigo.

Gastrointestinal: anorexia, constipation, dyspepsia,** dysphagia, diarrhea, flatulence, pancreatitis, vomiting, gingival hyperplasia.

General: allergic reaction, asthenia,** back pain, hot flushes, malaise, pain, rigors, weight gain, weight decrease.

Musculoskeletal System: arthralgia, arthrosis, muscle cramps,** myalgia.

Psychiatric: sexual dysfunction (male** and female), insomnia, nervousness, depression, abnormal dreams, anxiety, depersonalization.

Respiratory System: dyspnea,** epistaxis.

Skin and Appendages: angioedema, erythema multiforme, pruritus,** rash,** rash erythematous, rash maculopapular.

**These events occurred in less than 1% in placebo-controlled trials, but the incidence of these side effects was between 1% and 2% in all multiple dose studies.

Special Senses: abnormal vision, conjunctivitis, diplopia, eye pain, tinnitus.

Urinary System: micturition frequency, micturition disorder, nocturia.

Autonomic Nervous System: dry mouth, sweating increased.

Metabolic and Nutritional: hyperglycemia, thirst.

Hemopoietic: leukopenia, purpura, thrombocytopenia.

The following events occurred in ≤0.1% of patients treated with amlodipine in controlled clinical trials or under conditions of open trials or marketing experience: cardiac failure, pulse irregularity, extrasystoles, skin discoloration, urticaria, skin dryness, alopecia, dermatitis, muscle weakness, twitching, ataxia, hypertonia, migraine, cold and clammy skin, apathy, agitation, amnesia, gastritis, increased appetite, loose stools, coughing, rhinitis, dysuria, polyuria, parosmia, taste perversion, abnormal visual accommodation, and xerophthalmia.

Other reactions occurred sporadically and cannot be distinguished from medications or concurrent disease states such as myocardial infarction and angina.

Amlodipine therapy has not been associated with clinically significant changes in routine laboratory tests. No clinically relevant changes were noted in serum potassium, serum glucose, total triglycerides, total cholesterol, HDL cholesterol, uric acid, blood urea nitrogen, or creatinine.

In the CAMELOT and PREVENT studies (see **CLINICAL PHARMACOLOGY Clinical Studies, *Clinical Studies with Amlodipine)*** the adverse event profile was similar to that reported previously (see above), with the most common adverse event being peripheral edema.

The following postmarketing event has been reported infrequently with amlodipine treatment where a causal relationship is uncertain: gynecomastia. In postmarketing experience, jaundice and hepatic enzyme elevations (mostly consistent with cholestasis or hepatitis) in some cases severe enough to require hospitalization have been reported in association with use of amlodipine.

Amlodipine has been used safely in patients with chronic obstructive pulmonary disease, well-compensated congestive heart failure, peripheral vascular disease, diabetes mellitus, and abnormal lipid profiles.

The Atorvastatin Component of CADUET

Atorvastatin is generally well-tolerated. Adverse reactions have usually been mild and transient. In controlled clinical studies of 2502 patients, <2% of patients were discontinued due to adverse experiences attributable to atorvastatin calcium. The most frequent adverse events thought to be related to atorvastatin calcium were constipation, flatulence, dyspepsia, and abdominal pain.

Clinical Adverse Experiences

Adverse experiences reported in ≥2% of patients in placebo-controlled clinical studies of atorvastatin, regardless of causality assessment, are shown in Table 11.

Table 11. Adverse Events in Placebo-Controlled Studies
(% of Patients)

		atorvastatin			
Body System/ Adverse Event	**Placebo N=270**	**10 mg N=863**	**20 mg N=36**	**40 mg N=79**	**80 mg N=94**
BODY AS A WHOLE					
Infection	10.0	10.3	2.8	10.1	7.4
Headache	7.0	5.4	16.7	2.5	6.4
Accidental Injury	3.7	4.2	0.0	1.3	3.2
Flu Syndrome	1.9	2.2	0.0	2.5	3.2
Abdominal Pain	0.7	2.8	0.0	3.8	2.1
Back Pain	3.0	2.8	0.0	3.8	1.1
Allergic Reaction	2.6	0.9	2.8	1.3	0.0
Asthenia	1.9	2.2	0.0	3.8	0.0
DIGESTIVE SYSTEM					
Constipation	1.8	2.1	0.0	2.5	1.1
Diarrhea	1.5	2.7	0.0	3.8	5.3
Dyspepsia	4.1	2.3	2.8	1.3	2.1
Flatulence	3.3	2.1	2.8	1.3	1.1

RESPIRATORY SYSTEM					
Sinusitis	2.6	2.8	0.0	2.5	6.4
Pharyngitis	1.5	2.5	0.0	1.3	2.1
SKIN AND APPENDAGES					
Rash	0.7	3.9	2.8	3.8	1.1
MUSCULOSKELETAL SYSTEM					
Arthralgia	1.5	2.0	0.0	5.1	0.0
Myalgia	1.1	3.2	5.6	1.3	0.0

Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT)
In ASCOT (see **CLINICAL PHARMACOLOGY, Clinical Studies,** ***Clinical Studies with Atorvastatin***) involving 10,305 participants treated with atorvastatin 10 mg daily (n=5,168) or placebo (n=5,137), the safety and tolerability profile of the group treated with atorvastatin was comparable to that of the group treated with placebo during a median of 3.3 years of follow-up.

Collaborative Atorvastatin Diabetes Study (CARDS)
In CARDS (see **CLINICAL PHARMACOLOGY, Clinical Studies,** ***Clinical Studies with Atorvastatin***) involving 2838 subjects with type 2 diabetes treated with LIPITOR 10 mg daily (n=1428) or placebo (n=1410), there was no difference in the overall frequency of adverse events or serious adverse events between the treatment groups during a median follow-up of 3.9 years. No cases of rhabdomyolysis were reported.

The following adverse events were reported, regardless of causality assessment, in patients treated with atorvastatin in clinical trials. The events in italics occurred in ≥2% of patients and the events in plain type occurred in <2% of patients.

Body as a Whole: *Chest pain*, face edema, fever, neck rigidity, malaise, photosensitivity reaction, generalized edema.

Digestive System: *Nausea*, gastroenteritis, liver function tests abnormal, colitis, vomiting, gastritis, dry mouth, rectal hemorrhage, esophagitis, eructation, glossitis, mouth ulceration, anorexia, increased appetite, stomatitis, biliary pain, cheilitis, duodenal ulcer, dysphagia, enteritis, melena, gum hemorrhage, stomach ulcer, tenesmus, ulcerative stomatitis, hepatitis, pancreatitis, cholestatic jaundice.

Respiratory System: *Bronchitis*, *rhinitis*, pneumonia, dyspnea, asthma, epistaxis.

Nervous System: *Insomnia*, *dizziness*, paresthesia, somnolence, amnesia, abnormal dreams, libido decreased, emotional lability, incoordination, peripheral neuropathy, torticollis, facial paralysis, hyperkinesia, depression, hypesthesia, hypertonia.

Musculoskeletal System: *Arthritis*, leg cramps, bursitis, tenosynovitis, myasthenia, tendinous contracture, myositis.

Skin and Appendages: Pruritus, contact dermatitis, alopecia, dry skin, sweating, acne, urticaria, eczema, seborrhea, skin ulcer.

Urogenital System: *Urinary tract infection, hematuria, albuminuria,* urinary frequency, cystitis, impotence, dysuria, kidney calculus, nocturia, epididymitis, fibrocystic breast, vaginal hemorrhage, breast enlargement, metrorrhagia, nephritis, urinary incontinence, urinary retention, urinary urgency, abnormal ejaculation, uterine hemorrhage.

Special Senses: Amblyopia, tinnitus, dry eyes, refraction disorder, eye hemorrhage, deafness, glaucoma, parosmia, taste loss, taste perversion.

Cardiovascular System: Palpitation, vasodilatation, syncope, migraine, postural hypotension, phlebitis, arrhythmia, angina pectoris, hypertension.

Metabolic and Nutritional Disorders: *Peripheral edema*, hyperglycemia, creatine phosphokinase increased, gout, weight gain, hypoglycemia.

Hemic and Lymphatic System: Ecchymosis, anemia, lymphadenopathy, thrombocytopenia, petechia.

Postintroduction Reports with Atorvastatin

Adverse events associated with atorvastatin therapy reported since market introduction, that are not listed above, regardless of causality assessment, include the following: anaphylaxis, angioneurotic edema, bullous rashes (including erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis), rhabdomyolysis, fatigue and tendon rupture.

Pediatric Patients (ages 10-17 years)

In a 26-week controlled study in boys and postmenarchal girls (n=140), the safety and tolerability profile of atorvastatin 10 to 20 mg daily was generally similar to that of placebo (see **CLINICAL PHARMACOLOGY, Clinical Studies** section and **PRECAUTIONS, Pediatric Use**).

OVERDOSAGE

There is no information on overdosage with CADUET in humans.

Information on Amlodipine

Single oral doses of amlodipine maleate equivalent to 40 mg amlodipine/kg and 100 mg amlodipine/kg in mice and rats, respectively, caused deaths. Single oral amlodipine maleate doses equivalent to 4 or more mg amlodipine/kg in dogs (11 or more times the maximum

recommended clinical dose on a mg/m^2 basis) caused a marked peripheral vasodilation and hypotension.

Overdosage might be expected to cause excessive peripheral vasodilation with marked hypotension and possibly a reflex tachycardia. In humans, experience with intentional overdosage of amlodipine is limited. Reports of intentional overdosage include a patient who ingested 250 mg and was asymptomatic and was not hospitalized; another (120 mg) was hospitalized, underwent gastric lavage and remained normotensive; the third (105 mg) was hospitalized and had hypotension (90/50 mmHg) which normalized following plasma expansion. A patient who took 70 mg amlodipine and an unknown quantity of benzodiazepine in a suicide attempt developed shock which was refractory to treatment and died the following day with abnormally high benzodiazepine plasma concentration. A case of accidental drug overdose has been documented in a 19-month-old male who ingested 30 mg amlodipine (about 2 mg/kg). During the emergency room presentation, vital signs were stable with no evidence of hypotension, but a heart rate of 180 bpm. Ipecac was administered 3.5 hours after ingestion and on subsequent observation (overnight) no sequelae were noted.

If massive overdose should occur, active cardiac and respiratory monitoring should be instituted. Frequent blood pressure measurements are essential. Should hypotension occur, cardiovascular support including elevation of the extremities and the judicious administration of fluids should be initiated. If hypotension remains unresponsive to these conservative measures, administration of vasopressors (such as phenylephrine) should be considered with attention to circulating volume and urine output. Intravenous calcium gluconate may help to reverse the effects of calcium entry blockade. As amlodipine is highly protein bound, hemodialysis is not likely to be of benefit.

Information on Atorvastatin

There is no specific treatment for atorvastatin overdosage. In the event of an overdose, the patient should be treated symptomatically, and supportive measures instituted as required. Due to extensive drug binding to plasma proteins, hemodialysis is not expected to significantly enhance atorvastatin clearance.

DOSAGE AND ADMINISTRATION

Dosage of CADUET must be individualized on the basis of both effectiveness and tolerance for each individual component in the treatment of hypertension/angina and hyperlipidemia.

Amlodipine (Hypertension or angina)

Adults: The usual initial antihypertensive oral dose of amlodipine is 5 mg once daily with a maximum dose of 10 mg once daily. Small, fragile, or elderly individuals, or patients

with hepatic insufficiency may be started on 2.5 mg once daily and this dose may be used when adding amlodipine to other antihypertensive therapy.

Dosage should be adjusted according to each patient's need. In general, titration should proceed over 7 to 14 days so that the physician can fully assess the patient's response to each dose level. Titration may proceed more rapidly, however, if clinically warranted, provided the patient is assessed frequently.

The recommended dose of amlodipine for chronic stable or vasospastic angina is 5-10 mg, with the lower dose suggested in the elderly and in patients with hepatic insufficiency. Most patients will require 10 mg for adequate effect. See **ADVERSE REACTIONS** section for information related to dosage and side effects.

The recommended dose range of amlodipine for patients with coronary artery disease is 5-10 mg once daily. In clinical studies the majority of patients required 10 mg (see **CLINICAL PHARMACOLOGY, Clinical studies**).

Children: The effective antihypertensive oral dose of amlodipine in pediatric patients ages 6-17 years is 2.5 mg to 5 mg once daily. Doses in excess of 5 mg daily have not been studied in pediatric patients. See **CLINICAL PHARMACOLOGY**.

Atorvastatin (Hyperlipidemia)

The patient should be placed on a standard cholesterol-lowering diet before receiving atorvastatin and should continue on this diet during treatment with atorvastatin.

Hypercholesterolemia (Heterozygous Familial and Nonfamilial) and Mixed Dyslipidemia (Fredrickson* Types IIa and IIb*)
The recommended starting dose of atorvastatin is 10 or 20 mg once daily. Patients who require a large reduction in LDL-C (more than 45%) may be started at 40 mg once daily. The dosage range of atorvastatin is 10 to 80 mg once daily. Atorvastatin can be administered as a single dose at any time of the day, with or without food. The starting dose and maintenance doses of atorvastatin should be individualized according to patient characteristics such as goal of therapy and response (see *NCEP Guidelines,* summarized in Table 8). After initiation and/or upon titration of atorvastatin, lipid levels should be analyzed within 2 to 4 weeks and dosage adjusted accordingly.

Since the goal of treatment is to lower LDL-C, the NCEP recommends that LDL-C levels be used to initiate and assess treatment response. Only if LDL-C levels are not available, should total-C be used to monitor therapy.

Heterozygous Familial Hypercholesterolemia in Pediatric Patients (10-17 years of age)
The recommended starting dose of atorvastatin is 10 mg/day; the maximum recommended dose is 20 mg/day (doses greater than 20 mg have not been studied in this patient population). Doses should be individualized according to the recommended goal of therapy

(see NCEP Pediatric Panel Guidelines[1], **CLINICAL PHARMACOLOGY**, and **INDICATIONS AND USAGE**). Adjustments should be made at intervals of 4 weeks or more.

Homozygous Familial Hypercholesterolemia
The dosage of atorvastatin in patients with homozygous FH is 10 to 80 mg daily. Atorvastatin should be used as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) in these patients or if such treatments are unavailable. Note: a 2.5/80 mg CADUET tablet is not available. Management of patients needing a 2.5/80 mg combination requires individual assessments of dyslipidemia and therapy with the individual components as a 2.5/80 mg CADUET tablet is not available.

Concomitant Therapy
Atorvastatin may be used in combination with a bile acid binding resin for additive effect. The combination of HMG-CoA reductase inhibitors and fibrates should generally be avoided (see **WARNINGS, Skeletal Muscle**, and **PRECAUTIONS, Drug Interactions** for other drug-drug interactions).

Dosage in Patients With Renal Insufficiency
Renal disease does not affect the plasma concentrations nor LDL-C reduction of atorvastatin; thus, dosage adjustment in patients with renal dysfunction is not necessary (see **CLINICAL PHARMACOLOGY, Pharmacokinetics**).

CADUET

CADUET may be substituted for its individually titrated components. Patients may be given the equivalent dose of CADUET or a dose of CADUET with increased amounts of amlodipine, atorvastatin or both for additional antianginal effects, blood pressure lowering, or lipid lowering effect.

CADUET may be used to provide additional therapy for patients already on one of its components. As initial therapy for one indication and continuation of treatment of the other, the recommended starting dose of CADUET should be selected based on the continuation of the component being used and the recommended starting dose for the added monotherapy.

CADUET may be used to initiate treatment in patients with hyperlipidemia and either hypertension or angina. The recommended starting dose of CADUET should be based on the appropriate combination of recommendations for the monotherapies. The maximum dose of the amlodipine component of CADUET is 10 mg once daily. The maximum dose of the atorvastatin component of CADUET is 80 mg once daily.

See above for detailed information related to the dosing and administration of amlodipine and atorvastatin.

---

[1] National Cholesterol Education Program (NCEP): Highlights of the Report of the Expert Panel on Blood Cholesterol Levels in Children Adolescents. *Pediatrics*. 89(3):495-501. 1992.

HOW SUPPLIED

CADUET® tablets contain amlodipine besylate and atorvastatin calcium equivalent to amlodipine and atorvastatin in the dose strengths described below.

CADUET tablets are differentiated by tablet color/size and are engraved with "Pfizer" on one side and a unique number on the other side. CADUET tablets are supplied for oral administration in the following strengths and package configurations:

Table 12. CADUET Packaging Configurations

CADUET				
Package Configuration	Tablet Strength (amlodipine besylate/ atorvastatin calcium) mg	NDC #	Engraving	Tablet Color
Bottle of 30	2.5/10	0069-2960-30	CDT 251	White
Bottle of 30	2.5/20	0069-2970-30	CDT 252	White
Bottle of 30	2.5/40	0069-2980-30	CDT 254	White
Bottle of 30	5/10	0069-2150-30	CDT 051	White
Bottle of 30	5/20	0069-2170-30	CDT 052	White
Bottle of 30	5/40	0069-2190-30	CDT 054	White
Bottle of 30	5/80	0069-2260-30	CDT 058	White
Bottle of 30	10/10	0069-2160-30	CDT 101	Blue
Bottle of 30	10/20	0069-2180-30	CDT 102	Blue
Bottle of 30	10/40	0069-2250-30	CDT 104	Blue
Bottle of 30	10/80	0069-2270-30	CDT 108	Blue

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

Rx only

Manufactured by:
Pfizer Ireland Pharmaceuticals
Dublin, Ireland

Distributed by
Pfizer Labs
Division of Pfizer Inc, NY, NY 10017

LAB-0276-10.0
REVISED DECEMBER 2006

EXHIBIT H

PFIZER, INC.
235 East 42nd Street
Mailstop 235/10/45
New York, New York 10017

As of April 13, 2006

Robert Jarvik, M.D.
c/o Jarvik Heart Inc.
333 West 52nd Street
New York, NY 10019

Dear Dr. Jarvik:

The following will constitute the agreement (the "Agreement") between Robert Jarvik, M.D. ("Artist") and Pfizer, Inc. ("Company"), by which Artist agrees to provide his personal services as, among other things, an on-camera spokesperson for and endorsing Company's product known as Lipitor® (atorvastatin calcium) ("Product") and otherwise appear in and in connection with the production of advertising, sales, informational, promotion, marketing and publicity materials for the Product, upon the following terms and conditions:

*** *MATERIAL REDACTED* ***

*** *MATERIAL REDACTED* ***

Very truly yours,

Pfizer, Inc.

By: _____

ACCEPTED AND AGREED:

Robert Jarvik, M.D.

_____

Title: _____

Date: 6/15/06

EXHIBIT I

NEWS RELEASE

Committee on Energy and Commerce
Rep. John D. Dingell, Chairman

For Immediate Release: January 7, 2008
Contact: Jodi Seth or Brin Frazier, 202-225-5735

Committee Opens Investigation into Celebrity Drug Endorsements

Washington, D.C. - Reps. John D. Dingell (D-MI), Chairman of the Committee on Energy and Commerce, and Bart Stupak (D-MI), Chairman of the Subcommittee on Oversight and Investigations, announced today that they are opening an investigation into the use of celebrity endorsements of prescription medications in direct-to-consumer advertising, specific to Dr. Robert Jarvik's appearance in Pfizer's Lipitor Commercials.

"We are concerned that consumers might be misled by Pfizer's television ads for Lipitor starring Dr. Jarvik," said Dingell. "In the ads, Dr. Jarvik appears to be giving medical advice, but apparently, he has never obtained a license to practice or prescribe medicine."

"Dr. Jarvik's appearance in the ads could influence consumers into taking the medical advice of someone who may not be licensed to practice medicine in the United States," said Stupak. "Americans with heart disease should make medical decisions based on consultations with their doctors, not on paid advertisements during a commercial break."

Read the letter PDF

Prepared by the Committee on Energy and Commerce
2125 Rayburn House Office Building, Washington, DC 20515

EXHIBIT J

ONE HUNDRED TENTH CONGRESS

U.S. House of Representatives
Committee on Energy and Commerce
Washington, DC 20515–6115

JOHN D. DINGELL, MICHIGAN
CHAIRMAN

January 7, 2008

Mr. Jeffrey B. Kindler
Chairman of the Board, CEO
Pfizer, Inc.
235 East 42nd Street
New York, NY 10017

Dear Mr. Kindler:

Under Rules X and XI of the Rules of the U.S. House of Representatives, the Committee on Energy and Commerce and the Subcommittee on Oversight and Investigations are investigating the use of celebrity endorsements of prescription medications in direct-to-consumer advertising.

We are aware of television advertisements for Pfizer's Lipitor with Dr. Robert Jarvik, who appears to state in the advertisement that he takes Lipitor. We are concerned that consumers may misinterpret the health claims of a prescription drug promoted in a direct-to-consumer advertisement utilizing a celebrity physician. We are also concerned that Dr. Jarvik's qualifications may be misinterpreted in this advertisement campaign given that he may not be a practicing physician with a valid license in any State.

Therefore, we ask that you provide the following:

1. Any and all records relating to the advertisement campaign for Lipitor, including but not limited to, all contracts, e-mails, correspondence, and scripts for all television and print advertisements with Dr. Jarvik;

2. All records relating to Dr. Jarvik's association with Pfizer, including any contractual arrangements relating to his appearance in any Lipitor advertisements;

3. All financial records relating to Dr. Jarvik's association with Pfizer, including how much money he or any member of his family or any business entity associated with him or any member of his family has ever received from Pfizer, its subsidiaries, contractors or subcontractors;

4. Any records relating to the veracity of any claims made by Dr. Jarvik in any of the advertisements on behalf of Pfizer, including but not limited to, his use of Lipitor. Said request includes any due diligence done on behalf of Pfizer or its contractors, including any medical records indicating Dr. Jarvik's specific diagnosis and purpose for using the drug; and

5. All records relating to Dr. Jarvik's professional qualifications and why Pfizer chose him as their spokesman for Lipitor.

In addition, we ask that you do not destroy, dispose of, or tamper with any records relating to Dr. Jarvik and his association with Pfizer until the conclusion of this inquiry and that you notify all contractors involved in this advertisement campaign of this preservation request.

Please deliver copies of the requested records to the Subcommittee on Oversight and Investigations of the Committee on Energy and Commerce; Room 316, Ford House Office Building, no later than two weeks from the date of this letter. Please note that for the purpose of responding to this request, the terms "record" and "relating" should be interpreted in accordance with the attachment to this letter. After review of the records, we may require additional records and/or staff interviews with Pfizer officers, employees, or with Dr. Jarvik.

Thank you for your prompt attention to this matter. If you have any questions related to this request, please contact us or have your staff contact John F. Sopko or Paul Jung of the Committee staff at (202) 226-2424.

Sincerely,

John D. Dingell
Chairman

Bart Stupak
Chairman
Subcommittee on Oversight and Investigations

Attachment

cc: The Honorable Joe Barton, Ranking Member
Committee on Energy and Commerce

The Honorable John Shimkus, Ranking Member
Subcommittee on Oversight and Investigations

ATTACHMENT

1. The term "records" is to be construed in the broadest sense and shall mean any written or graphic material, however produced or reproduced, of any kind or description, consisting of the original and any non-identical copy (whether different from the original because of notes made on or attached to such copy or otherwise) and drafts and both sides thereof, whether printed or recorded electronically or magnetically or stored in any type of data bank, including, but not limited to, the following: correspondence, memoranda, records, summaries of personal conversations or interviews, minutes or records of meetings or conferences, opinions or reports of consultants, projections, statistical statements, drafts, contracts, agreements, purchase orders, invoices, confirmations, telegraphs, telexes, agendas, books, notes, pamphlets, periodicals, reports, studies, evaluations, opinions, logs, diaries, desk calendars, appointment books, tape recordings, video recordings, e-mails, voice mails, computer tapes, or other computer stored matter, magnetic tapes, microfilm, microfiche, punch cards, all other records kept by electronic, photographic, or mechanical means, charts, photographs, notebooks, drawings, plans, inter-office communications, intra-office and intra-departmental communications, transcripts, checks and canceled checks, bank statements, ledgers, books, records or statements of accounts, and papers and things similar to any of the foregoing, however denominated.

2. The terms "relating," or "relate" as to any given subject means anything that constitutes, contains, embodies, identifies, deals with, or is in any manner whatsoever pertinent to that subject, including but not limited to records concerning the preparation of other records.

EXHIBIT K

The New York Times
nytimes.com

February 25, 2008

Pfizer to End Lipitor Campaign by Jarvik

By STEPHANIE SAUL

Under criticism that its ads are misleading, Pfizer said Monday it would cancel a long-running advertising campaign using the artificial heart pioneer Dr. Robert Jarvik as a spokesman for its cholesterol drug Lipitor.

Pfizer has spent more than $258 million advertising Lipitor since January 2006, most of it on the Jarvik campaign, as the company sought to protect Lipitor, the world's best-selling drug, from competition by cheaper generics.

But the campaign had come under scrutiny from a Congressional committee that is examining consumer drug advertising and has asked whether the ads misrepresented Dr. Jarvik and his credentials. Although he has a medical degree, Dr. Jarvik is not a cardiologist and is not licensed to practice medicine.

One television ad depicted Dr. Jarvik as an accomplished rower gliding across a mountain lake, but the ad used a body double for the doctor, who apparently does not row.

"The way in which we presented Dr. Jarvik in these ads has, unfortunately, led to mis-impressions and distractions from our primary goal of encouraging patient and physician dialogue on the leading cause of death in the world — cardiovascular disease," Pfizer's president of worldwide pharmaceutical operations, Ian Read, said in a statement. "We regret this. Going forward, we commit to ensuring there is greater clarity in our advertising regarding the presentation of spokespeople."

A company spokeswoman, Vanessa Aristide, said Pfizer was working with its advertising agency, the Kaplan Thaler Group, to develop a new campaign.

Lipitor, with sales of $12.7 billion last year, is protected by patent until 2010. Some patients have, nevertheless, begun switching to a generic version of a competing cholesterol drug, Zocor.

The House Energy and Commerce Committee has been looking into television ads featuring

Dr. Jarvik. The committee disclosed that Pfizer agreed to pay Dr. Jarvik at least $1.35 million under a two-year contract that expired next month. John D. Dingell, the Michigan Democrat who is chairman of that committee, raised questions about Dr. Jarvik's credentials to recommend Lipitor.

Dr. Jarvik, who has recently declined to discuss the Lipitor campaign, could not be reached for comment Monday.

The committee's investigation has rekindled a debate over the so-called direct-to-consumer advertising of pharmaceuticals, a $4.8 billion business. Mr. Dingell and Bart Stupak, another Michigan Democrat who heads an investigations subcommittee, applauded Pfizer's decision to pull the Lipitor ads.

"I commend Pfizer for doing the right thing and pulling the Lipitor ads featuring Dr. Jarvik," Mr. Stupak said in a statement. "When consumers see and hear a doctor endorsing medication, they expect the doctor is a credible individual with requisite knowledge of the drug."

While endorsing Pfizer's decision, the committee showed no sign of shutting down its investigation. Mr. Stupak said the committee planned to meet with Dr. Jarvik and collect all of the documents it had requested.

The committee had recently asked 10 advertising agencies that worked on the Dr. Jarvik campaign to submit documents about the use of body doubles. The committee has also contacted at least one former colleague of Dr. Jarvik's who contends that he was not the actual inventor of the artificial heart, as stated in the ads.

In a letter to Pfizer in August 2006, three former colleagues of Dr. Jarvik's at the University of Utah complained that the ads erroneously identified Dr. Jarvik as "inventor of the artificial heart." That distinction, they said, should go to Dr. Jarvik's mentor, Dr. Willem J. Kolff, and his associate, Dr. Tetsuzo Akutsu.

Pfizer subsequently changed its ads to identify Dr. Jarvik as the inventor of the "Jarvik artificial heart," but Dr. Jarvik's former colleagues, members of a large team that worked on the heart, were not entirely satisfied, according to Dr. Donald B. Olsen, a veterinarian who worked on the heart and is president of the Utah Artificial Heart Institute. Dr. Olsen said he was recently contacted by the committee.

A long-simmering dispute over assigning credit for the artificial heart boiled over again during a conference last December at the University of Utah. Dr. Jarvik did not attend the conference,

which marked the 25th anniversary of the heart's experimental use to extend the life of Dr. Barney Clark, a Seattle dentist.

During the meeting, another former Utah colleague of Dr. Jarvik's, Dr. Clifford S. Kwan-Gett, stated that the Jarvik series of hearts were simply different versions of prototypes that Dr. Kwan-Gett had made more than a year earlier.

Dr. Jarvik's company, Jarvik Heart, subsequently posted a history of the artificial heart's development on its Web site, giving his own account of the heart's development. That posting said Dr. Jarvik's design overcame two problems of the heart developed by Dr. Kwan-Gett.

Jarvik Heart, based in Manhattan, has been working for the last two decades on a continuous flow pump that can be inserted directly into a patient's damaged heart to bolster its function.

EXHIBIT L

NEWS RELEASE

Committee on Energy and Commerce
Rep. John D. Dingell, Chairman

For Immediate Release: February 25, 2008
Contact: Jodi Seth or Brin Frazier, 202-225-5735

Dingell, Stupak Comment on Pfizer Decision to Pull Lipitor Ads Featuring Dr. Jarvik

In Light of Committee Investigation, Pfizer Acknowledges that Ads "Created Misimpressions"

Washington, DC – Reps. John D. Dingell (D-MI), Chairman of the Committee on Energy and Commerce, and Bart Stupak, Chairman of the Subcommittee on Oversight and Investigations, today responded to news that Pfizer, Inc., is withdrawing Lipitor advertising and promotions featuring Dr. Robert Jarvik. The Committee launched an investigation into the use of celebrity endorsements of prescription medications in direct-to-consumer (DTC) advertising on January 7, 2007, by writing to Pfizer, Inc., regarding Dr. Jarvik's appearance in Lipitor commercials.

"Pfizer's decision was a wise one, and I am pleased our investigation prompted the removal of Lipitor ads featuring Dr. Jarvik," said Dingell. "We trust that Pfizer is sincere in its commitment to 'greater clarity' in its advertising. My colleagues and I look forward to meeting with Pfizer's management team to discuss their plans related to direct-to-consumer advertising."

Pfizer's Lipitor advertisements featuring Dr. Robert Jarvik represent the second ad campaign to be removed since the Committee began investigating DTC advertisements. Merck/Schering-Plough's "Food and Family" television ads for Vytorin have also been pulled.

"I commend Pfizer for doing the right thing and pulling the Lipitor ads featuring Dr. Jarvik," said Stupak. "When consumers see and hear a doctor endorsing medication, they expect the doctor is a credible individual with requisite knowledge of the drug. We will continue to investigate the deception that occurs in direct-to-consumer advertising of medications, including Pfizer's Lipitor campaign. We plan to meet with Dr. Jarvik, collect all of the documents we've requested and closely review the facts. Drug companies should know that they will be held accountable for the representations made in their ads."

Read January 7, 2008 Committee letter to Pfizer's CEO »
Read February 25, 2008 response letter from Pfizer »

- 30 -

Prepared by the Committee on Energy and Commerce
2125 Rayburn House Office Building, Washington, DC 20515